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<b>(54) Title:</b> LECTOMEDIN MATERIALS AND METHODS		
<b>(57) Abstract</b>  Disclosed are novel seven transmembrane receptor polypeptides having characteristic extracellular structure including lectin-binding, olfactomedin-like and mucin-like domains.		

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## LECTOMEDIN MATERIALS AND METHODS

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### **BACKGROUND OF THE INVENTION**

G-protein coupled receptors (GPCRs) are proteins that interact with G-proteins to transmit an intracellular signal. Upon ligand binding, GPCRs trigger the hydrolysis of GTP to GDP by G-protein subunits; GTP hydrolysis is accompanied by a switch from activity to inactivity. It is estimated that there are roughly 1,000 GPCRs [Clapham, *Nature* 379:297-299 (1996)] and all characterized to date include a seven transmembrane domain that anchors the receptor to the cell. GPCRs include receptors for opiates, adrenaline, histamine, polypeptide hormones, and photons, among other ligands. These receptors are coupled to a wide variety of cellular second messenger pathways including, for example, pathways that alter intracellular calcium concentrations and cAMP levels.

Among the various GPCRs identified, CD97 appears to be representative of a sub-family of proteins which effect cellular adhesion [McKnight, *et al.*, *Immunol Today* 17:283-287(1996)]. CD97 and related receptors are unique in that their structure includes a transmembrane domain that directly links a cytoplasmic domain that participates in GTP hydrolysis with extracellular protein binding domains that specifically participate in cell-cell adhesion. The extracellular, amino terminal region of CD97 includes numerous cell-cell adhesive motifs, including multiple epidermal growth factor-like (EGF-like) repeats and an integrin binding site [Hamann J, *et al.*, *Immunol* 155:1942-1950 (1996); Gray, *et al.*, *J. Immunol* 157:5438-5447 (1996)]. Proteins that contain EGF-like repeats have been shown to be involved in cell adhesion events [Campbell, *et al.*, *Curr. Opin. Struct. Biol.* 3:385-392 (1993); Rao, *et al.*, *Cell* 82:131-141 (1995)], and consistent with this observation, heterologous expression of CD97 in COS cells elicits homotypic cell aggregation that can be blocked in the presence of anti-CD97 monoclonal antibodies [Hamann, *et al.*, *J. Exp. Med.* 184:1185-1189 (1996)]. CD97 and related proteins have been referred to as the EGF-7TM subfamily of seven transmembrane receptors [McKnight and Gordon, *Immunol. Today* 17:283-2887 (1996)]. Ligands identified for

CD97 include members of the integrin family of cell surface adhesion receptors. Various integrins recognize and interact with their cognate ligands through a trimeric amino acid sequence of arginine-glycine-aspartic acid (denoted RGD in the single letter amino acid code) [D'Souza, *et al.*, *Trends Biochem. Sci.*, 16:246-250 (1991)] and this sequence has  
5 been identified in the extracellular region of CD97, between the EGF-like repeats and the transmembrane domain.

CD97 has been shown to undergo post-translational proteolytic processing which results in an extracellular (and potentially soluble) alpha subunit and a smaller, integral membrane beta subunit [Gray, *et al.*, *J. Immunol.* 157:5438-5447 (1996)]. The  
10 two subunits are associated in a non-covalent manner and the alpha subunit is held at the cell surface through its interaction with the beta subunit. The role of proteolysis is unclear, but it may be a mechanism for receptor down-regulation which is common among proteins, such as selectins and intercellular adhesion molecules (ICAMs), that participate in cell adhesion.

Other members of the CD97 sub-family of GPCRs have been identified by amino acid sequence and structural homology and include human EMR1, HE6, BAI1, the calcium-independent receptor of latrotoxin (CIRL), latrophilin, and proteins encoded by the *Caenorhabditis elegans* open reading frames designated B0457.1 and B0286.2 [Baud V, *et al.*, *Genomics* 26:334-344 (1995); McKnight, *et al.*, *J. Biol. Chem.* 271:486-489  
20 (1996); Krasnoperov, *et al.*, *Neuron* 18:925-937 (1997); Lelianaova, *et al.*, *J. Biol. Chem.* 272:21504-21508 (1997); Davletov, *et al.*, *J. Biol. Chem.* 271:23239-23245 (1996); Nishimori, *et al.*, *Oncogene* 15:2145-2150 (1997)]. EMR1, and its murine homolog F4/80, are macrophage-specific in expression and structurally related to CD97 in that they contain multiple extracellular EGF-like repeats, a rod-like stalk region, and the  
25 characteristic transmembrane domain of GPCRs [Baud V, *et al.*, *Genomics* 26:334-344 (1995); McKnight, *et al.*, *J. Biol. Chem.* 271:486-489 (1996)]. No ligands have been identified for EMR-1 and it is uncertain if the protein undergoes post-translational proteolytic processing.

CIRL [Krasnoperov, *et al.*, *Neuron* 18:925-937 (1997); Lelianaova, *et al.*,  
30 *J. Biol. Chem.* 272:21504-21508 (1997); Davletov, *et al.*, *J. Biol. Chem.* 271:23239-23245 (1996)] is believed to be expressed specifically in the central nervous system at

neuronal presynaptic terminals and, like CD97, undergoes proteolytic cleavage resulting in an extracellular alpha subunit in non-covalent association with an integral membrane seven-transmembrane beta subunit. Cleavage of latrophilin is believed to occur at a Ser-His-Leu/Thr-Asn-Phe site that is conserved in CD97 [Krasnoperov, *et al.*, *Neuron* 18:925-937 (1997)]. CIRL has been shown to bind latrotoxin, a component of black widow spider venom, in the 0.5 to 1.0 nM range, and binding of the ligand to CIRL expressed in bovine chromaffin cells has been shown to result in exocytosis, a hallmark of toxin binding [Krasnoperov, *et al.*, *Neuron* 18:925-937 (1997)]. Alpha latrotoxin binding has also been demonstrated at neuromuscular motor endplates, and this interaction elicits explosive secretory granule release of acetylcholine from presynaptic granules, resulting in muscle paralysis characteristic of the spider's bite [Petrenko, *et al.*, *F.E.B.S. Letts.* 325:81-85 (1993)]. It is unclear, however, if the peripheral toxin effects result from binding to CIRL or some other related protein.

Thus there exists a need in the art to identify and characterize other members of the CD97-like family of GPCRs, in particular human receptors which participate in cellular adhesion and those that participate in cytoplasmic metabolic pathways modulated by extracellular signals. Identification of CD97-like receptors can permit identification and diagnosis of disease states which arise from aberrant signaling by the receptor, as well as disease states that arise from aberrant expression of the receptor itself.

#### **SUMMARY OF THE INVENTION**

The present invention provides purified and isolated human seven transmembrane receptor lectomedin polypeptides or fragments thereof, said polypeptides comprising extracellular lectin-binding, olfactomedin-like, and mucin-like domains. Mature lectomedin polypeptides are also provided wherein signal or leader sequences are cleaved. Preferred polypeptides of the invention comprise the amino acid sequence set out in SEQ ID NO: 2 or a fragment thereof, the amino acid sequence set out in SEQ ID NO: 4 or fragment thereof, the amino acid sequence set out in SEQ ID NO: 6 or fragment thereof, and the amino acid sequence set out in SEQ ID NO: 58 or fragment thereof.

The invention also provides polynucleotides encoding polypeptides of the invention. Preferred polynucleotides comprising the sequence set forth in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, and SEQ ID NO: 57. The invention also provide polynucleotides encoding a human lectomedin polypeptide selected from the group consisting of the polynucleotide set out in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 57; b) a DNA which hybridizes under moderately stringent conditions to the non-coding strand of the polynucleotide of (a); and c) a DNA which would hybridize to the non-coding strand of the polynucleotide of (a) but for the redundancy of the genetic code. Preferred polynucleotides of the invention are DNA molecules. Preferred DNA molecules are cDNA molecules and genomic DNA molecules. The invention also provides DNA which is a wholly or partially chemically synthesized. Anti-sense polynucleotide which specifically hybridizes with a polynucleotide of the invention are also comprehended.

The invention also proved expression construct comprising the a polynucleotide of the invention, as well as host cells transformed or transfected with a polynucleotide or expression construct of the invention.

The invention also provides polynucleotide of the invention operably linked to a heterologous promoter, and host cells polynucleotides operably linked to a heterologous promoter.

In another aspect, the invention provides methods for producing a human lectomedin polypeptide comprising the steps of: a) growing the host cell of the invention under conditions appropriate for expression of the lectomedin polypeptide and b) isolating the lectomedin polypeptide from the host cell or the medium of its growth.

The invention also proved antibodies specifically immunoreactive with a polypeptide of the invention. Preferably, antibodies of the invention are monoclonal antibodies. The invention also provides cells, *e.g.* hybridomas, that produce antibodies of the invention. Anti-idiotypic antibodies specifically immunoreactive with an antibody of the invention are also comprehended.

The invention also provides methods to identify a specific binding partner compound of a lectomedin polypeptide comprising the steps of: a) contacting the lectomedin polypeptide with a compound under conditions which permit binding between

the compound and the lectomedin polypeptide; b) detecting binding of the compound to the lectomedin polypeptide; and c) identifying the compound as a specific binding partner of the lectomedin polypeptide. Methods of the invention embrace specific binding partner that modulate activity of the lectomedin polypeptide. In one aspect, the compound  
5 inhibits activity of the lectomedin polypeptide, and in another aspect, the compound enhances activity of the lectomedin polypeptide.

The invention also provides methods to identify a specific binding partner compound of a lectomedin polynucleotide comprising the steps of: a) contacting the lectomedin polynucleotide with a compound under conditions which permit binding  
10 between the compound and the lectomedin polynucleotide; b) detecting binding of the compound to the lectomedin polynucleotide; and c) identifying the compound as a specific binding partner of the lectomedin polynucleotide. Methods of the invention embrace specific binding partner that modulates expression of a lectomedin polypeptide encoded by the lectomedin polynucleotide. In one aspect, the compound inhibits  
15 expression of the lectomedin polypeptide, and in another aspect, the compound enhances expression of the lectomedin polypeptide. The invention also provides compounds identified by a method of the invention.

In another aspect, the invention comprehends composition comprising the compound identified by a method of the invention, and a pharmaceutically acceptable  
20 carrier. The invention also provides use of a compound identified by a method of the invention for the preparation of a medicament to treat lectomedin related pathologies.

The invention also provides for use of a lectomedin polypeptide in the preparation of a medicament for the treatment of a lectomedin related disorder.

## 25 **DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides purified and isolated polypeptides and underlying polynucleotides for a novel family of transmembrane proteins designated lectomedins. The invention includes both naturally occurring and non-naturally occurring lectomedin polynucleotides and polypeptide products thereof. Naturally occurring  
30 lectomedin products include distinct gene and polypeptide species within the lectomedin family, including, for example, allelic variants, which are expressed within cells of the

same animal, as well as corresponding species homologs expressed in cells of other animals. The invention further provides splice variants encoded by the same polynucleotide but which arise from distinct mRNA transcripts. Non-naturally occurring lectomedin products include variants of the naturally occurring products such as analogs, fragments, fusion (or chimeric) proteins, and lectomedin products having covalent modifications. The lectomedin family of proteins is distinguished from previously known seven transmembrane families of proteins in that the lectomedin proteins include at least one extracellular lectin binding-like domain and at least one extracellular olfactomedin domain. Unlike many other seven transmembrane proteins, the structure of proteins in the lectomedin family of proteins does not include EGF-like binding domains which effect cell/cell interactions. In a preferred embodiment, the invention provides polynucleotides comprising the sequences set forth in SEQ ID NOs: 1, 3, 5 and 57. The invention also embraces polynucleotides encoding the amino acid sequences set out in SEQ ID NOs: 2, 4, 6, and 58. Presently preferred polypeptides of the invention comprises the amino acid sequences set out in SEQ ID NOs: 2, 4, 6, and 58.

The invention also provides expression constructs (or vectors) comprising polynucleotides of the invention, as well as host cells transformed, transfected, or electroporated to include a polynucleotide or expression construct of the invention. Methods to produce a polypeptide of the invention are also comprehended. The invention further provides antibodies, preferably monoclonal antibodies, specifically immunoreactive with a polypeptide of the invention, as well as cell lines, *e.g.*, hybridomas, that secrete the antibodies.

The present invention provides novel purified and isolated human polynucleotides (*e.g.*, DNA sequences and RNA transcripts, both sense and complementary antisense strands, including splice variants thereof) encoding the human lectomedins. DNA sequences of the invention include genomic and cDNA sequences as well as wholly or partially chemically synthesized DNA sequences. Genomic DNA of the invention comprises the protein coding region for a polypeptide of the invention and includes allelic variants of the preferred polynucleotides of the invention. Genomic DNA of the invention is distinguishable from genomic DNAs encoding polypeptides other than lectomedin in that it includes the lectomedin coding region found in lectomedin cDNA of



the invention. Genomic DNA of the invention can be transcribed into RNA, and the resulting RNA transcript may undergo one or more splicing events wherein one or more introns (*i.e.*, non-coding regions) of the transcript are removed, or "spliced out." RNA transcripts that can be spliced by alternative mechanisms, and therefore be subjected to removal of different non-coding RNA sequences but still encode a lectomedin polypeptide, are referred to in the art as splice variants, which are embraced by the invention. Splice variants comprehended by the invention, therefore, are encoded by the same DNA sequences but arise from distinct mRNA transcripts. Allelic variants are known in the art to be modified forms of a wild type (predominant) gene sequence, the modification resulting from recombination during chromosomal segregation or exposure to conditions which give rise to genetic mutation. Allelic variants, like wild type genes, are inherently naturally occurring sequences (as opposed to non-naturally occurring variants which arise from *in vitro* manipulation).

The invention also comprehends cDNA that is obtained through reverse transcription of an RNA polynucleotide encoding lectomedin, followed by second strand synthesis of a complementary strand to provide a double stranded DNA.

"Chemically synthesized" as used herein and understood in the art, refers to polynucleotides produced by purely chemical, as opposed to enzymatic, methods. "Wholly" synthesized DNA sequences are therefore produced entirely by chemical means, and "partially" synthesized DNAs embrace those wherein only portions of the resulting DNA were produced by chemical means.

Preferred DNA sequences encoding human lectomedin polypeptides are set out in SEQ ID NOs: 1, 3, 5, and 57. The worker of skill in the art will readily appreciate that preferred DNAs of the invention comprise double stranded molecules, for example, the molecule having the sequence set forth in either SEQ ID NOs: 1, 3, 5, or 57, along with the complementary molecule (the "non-coding strand" or "complement") having a sequence deducible from the sequence of SEQ ID NO: 1 according to Watson-Crick base pairing rules for DNA. Also preferred are polynucleotides encoding the lectomedin polypeptides of SEQ ID NOs: 2, 4, 6, and 58.

The invention further embraces species, preferably mammalian, homologs of the human lectomedin DNA. Species homologs, in general, share at least 35%, at least

40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%,  
at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99%  
homology with human DNA of the invention. Percent sequence "homology" with respect  
to polynucleotides of the invention is defined herein as the percentage of nucleotide bases  
in the candidate sequence that are identical to nucleotides in the lectomedin coding  
sequence after aligning the sequences and introducing gaps, if necessary, to achieve the  
maximum percent sequence identity.

The polynucleotide sequence information provided by the invention makes  
possible large scale expression of the encoded polypeptide by techniques well known and  
routinely practiced in the art. Polynucleotides also permit identification and isolation of  
polynucleotides encoding related lectomedin polypeptides by well known techniques  
including Southern and/or Northern hybridization, and polymerase chain reaction (PCR),  
ligase chain reaction, as well as other amplification techniques. Examples of related  
polynucleotides include human and non-human genomic sequences, including allelic  
variants, as well as polynucleotides encoding polypeptides homologous to lectomedins and  
structurally related polypeptides sharing one or more biological, immunological, and/or  
physical properties of lectomedin.

The disclosure of full length polynucleotides encoding lectomedin  
polypeptides makes readily available to the worker of ordinary skill in the art every  
possible fragment of the full length polynucleotides. The invention therefore provides  
fragments of lectomedin coding polynucleotides. Such fragments comprise at least 10 to  
20, and preferably at least 15, consecutive nucleotides of the polynucleotide. The  
invention comprehends, however, fragments of various lengths. Preferably, fragment  
polynucleotides of the invention comprise sequences unique to the lectomedin coding  
polynucleotide sequence, and therefore hybridize under highly stringent or moderately  
stringent conditions only (*i.e.*, "specifically") to polynucleotides encoding lectomedin, or  
lectomedin fragments thereof containing the unique sequence. Polynucleotide fragments  
of genomic sequences of the invention comprise not only sequences unique to the coding  
region, but also include fragments of the full length sequence derived from introns,  
regulatory regions, and/or other non-translated sequences. Sequences unique to  
polynucleotides of the invention are recognizable through sequence comparison to other

known polynucleotides, and can be identified through use of alignment programs routinely utilized in the art, *e.g.*, those made available in public sequence databases.

The invention also provides fragment polynucleotides that are conserved in one or more polynucleotides encoding members of the lectomedin family of polypeptides. Such fragments include sequences characteristic of the family of lectomedin polynucleotides, and are also referred to as "signature sequences." The conserved signature sequences are readily discernable following simple sequence comparison of polynucleotides encoding members of the lectomedin family. Fragments of the invention can be labeled in a manner that permits their detection, including radioactive and non-radioactive labeling.

Fragment polynucleotides are particularly useful as probes for detection of full length or other fragment lectomedin coding polynucleotides. One or more fragment polynucleotides can be included in kits that are used to detect the presence of a polynucleotide encoding lectomedin, or used to detect variations in a polynucleotide sequence encoding lectomedin.

The invention also embraces DNA sequences encoding lectomedin species which hybridize under moderately or highly stringent conditions to the non-coding strand, or complement, of the polynucleotide in SEQ ID NOs: 1, 3, 5, or 57. DNA sequences encoding lectomedin polypeptides which would hybridize thereto but for the redundancy of the genetic code are further comprehended by the invention. Exemplary highly stringent conditions are include hybridization at 45°C in 5X SSPE and 45% formamide, and a final wash at 65°C in 0.1X SSC. Exemplary moderately stringent condition include a final wash at 55°C in 1X SSC. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described Ausubel, *et al.* (Eds.), Protocols in Molecular Biology, John Wiley & Sons (1994), pp. 6.0.3 to 6.4.10. Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, *et al.*, (Eds.), Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47 to 9.51.

Autonomously replicating recombinant expression constructs such as plasmid and viral DNA vectors incorporating lectomedin coding sequences are also provided. Expression constructs wherein lectomedin-encoding polynucleotides are operably linked to an endogenous or exogenous expression control DNA sequence and a transcription terminator are also provided. Expression control DNA sequences include promoters, enhancers, and operator, and are generally selected based on the expression systems in which the expression construct is to be utilized. Preferred promoter and enhancer sequences are generally selected for the ability to increase gene expression, while operator sequences are generally selected for the ability to regulate gene expression. Expression constructs of the invention may also include sequences encoding one or more selectable markers that permit identification of host cells bearing the construct. Expression constructs may also include sequences that facilitate, and preferably promote, homologous recombination in a host cell. Preferred constructs of the invention also include sequences necessary for replication in a host cell. Expression constructs are preferably utilized for production of an encoded lectomedin protein, but may also be utilized to amplify the construct itself.

According to another aspect of the invention, host cells are provided, including prokaryotic and eukaryotic cells, comprising a polynucleotide of the invention in a manner which permits expression of the encoded lectomedin polypeptide. Polynucleotides of the invention may be introduced into the host cell as part of a circular plasmid, or as linear DNA comprising an isolated protein coding region or a viral vector. Methods for introducing DNA into the host cell well known and routinely practiced in the art include transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts. Expression systems of the invention include bacterial, yeast, fungal, plant, insect, invertebrate, and mammalian cells systems. Host cells of the invention are a valuable source of immunogen for development of antibodies specifically immunoreactive with lectomedin. Host cells of the invention are also useful in methods for large scale production of lectomedin polypeptides wherein the cells are grown in a suitable culture medium and the desired polypeptide products are isolated from the cells or from the medium in which the cells are grown by purification methods known in the art, e.g., conventional chromatographic methods

including immunoaffinity chromatography, receptor affinity chromatography, hydrophobic interaction chromatography, lectin affinity chromatography, size exclusion filtration, cation or anion exchange chromatography, high pressure liquid chromatography (HPLC), reverse phase HPLC and the like. Still other methods of purification include those wherein the desired protein is expressed and purified as a fusion protein having a specific tag, label, or chelating moiety that is recognized by a specific binding partner or agent. The purified protein can be cleaved to yield the desired protein, or be left as an intact fusion protein. Cleavage of the fusion component may produce a form of the desired protein having additional amino acid residues as a result of the cleavage process.

Knowledge of lectomedin coding DNA sequences allows for modification of cells to permit, or increase, expression of endogenous lectomedin. Cells can be modified (*e.g.*, by homologous recombination) to provide increased lectomedin expression by replacing, in whole or in part, the naturally occurring lectomedin promoter with all or part of a heterologous promoter so that the cells express lectomedin at higher levels. The heterologous promoter is inserted in such a manner that it is operably linked to lectomedin- encoding sequences. See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (*e.g.*, *ada*, *dhfr*, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the lectomedin coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the lectomedin coding sequences in the cells.

The DNA sequence information provided by the present invention also makes possible the development through, *e.g.* homologous recombination or "knock-out" strategies [Capecchi, *Science* 244:1288-1292 (1989)], of animals that fail to express functional lectomedin or that express a variant of lectomedin. Such animals are useful as models for studying the *in vivo* activities of lectomedin and modulators of lectomedin.

The invention also provides purified and isolated mammalian lectomedin polypeptides encoded by a polynucleotide of the invention. Presently preferred are

lectomedin polypeptides comprising the amino acid sequence set out in SEQ ID NO: 2, 4, 6, or 58. The invention also embraces lectomedin polypeptides encoded by a DNA selected from the group consisting of: a) the DNA sequence set out in SEQ ID NO: 1, 3, 5 or 57; b) a DNA molecule which hybridizes under high stringent conditions to the noncoding strand of the protein coding portion of (a); and c) a DNA molecule that would hybridize to the DNA of (a) but for the degeneracy of the genetic code.

The invention also embraces variant (or analog) lectomedin polypeptides. In one example, insertion variants are provided wherein one or more amino acid residues supplement a lectomedin amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the lectomedin amino acid sequence. Insertional variants with additional residues at either or both termini can include for example, fusion proteins and proteins including amino acid tags or labels.

In another aspect, the invention provides deletion variants wherein one or more amino acid residues in a lectomedin polypeptide are removed. Deletions can be effected at one or both termini of the lectomedin polypeptide, or with removal of one or more residues within the lectomedin amino acid sequence. Deletion variants, therefore, include all fragments of a lectomedin polypeptide.

In still another aspect, the invention provides substitution variants of lectomedin polypeptides. Substitution variants include those polypeptides wherein one or more amino acid residues of a lectomedin polypeptide are removed and replaced with alternative residues. In one aspect, the substitutions are conservative in nature, however, the invention embraces substitutions that are also non-conservative. Conservative substitutions for this purpose may be defined as set out in Tables A, B, or C below.

The invention also provides derivatives of lectomedin polypeptides. Derivatives include lectomedin polypeptides bearing modifications other than insertion, deletion, or substitution of amino acid residues. Preferably, the modifications are covalent in nature, and include, for example, chemical bonding with polymers, lipids, non-naturally occurring amino acids, other organic, and inorganic moieties. Derivatives of the invention may be prepared to increase circulating half-life of a lectomedin polypeptide, or may be designed to improve targeting capacity for the polypeptide to desired cells, tissues, or organs.

The invention also embraces polypeptides have at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55% or at least 50% identity and/or homology to the preferred polypeptide of the invention. Percent amino acid sequence "identity" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the lectomedin sequence after aligning both sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Percent sequence "homology" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the lectomedin sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and also considering any conservative substitutions as part of the sequence identity.

In one aspect, percent homology is calculated as the percentage of amino acid residues in the smaller of two sequences which align with identical amino acid residue in the sequence being compared, when four gaps in a length of 100 amino acids may be introduced to maximize alignment [Dayhoff, in Atlas of Protein Sequence and Structure, Vol. 5, p. 124, National Biochemical Research Foundation, Washington, D.C. (1972), incorporated herein by reference].

Polypeptides of the invention may be isolated from natural cell sources or may be chemically synthesized, but are preferably produced by recombinant procedures involving host cells of the invention. Use of mammalian host cells is expected to provide for such post-translational modifications (*e.g.*, glycosylation, truncation, lipidation, and phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the invention. Glycosylated and non-glycosylated form of lectomedin polypeptides are embraced.

Insertion variants include lectomedin polypeptides wherein one or more amino acid residues are added to a lectomedin acid sequence, or fragment thereof. Variant products of the invention also include mature lectomedin products, *i.e.*, lectomedin products wherein leader or signal sequences are removed, with additional

amino terminal residues. The additional amino terminal residues may be derived from another protein, or may include one or more residues that are not identifiable as being derived from a specific proteins. Lectomedin products with an additional methionine residue at position -1 (Met<sup>-1</sup>-lectomedin) are contemplated, as are lectomedin products with additional methionine and lysine residues at positions -2 and -1 (Met<sup>-2</sup>-Lys<sup>-1</sup>-lectomedin). Variants of lectomedin with multiple, additional Met, Met-Lys, Lys residues are particularly useful for enhanced recombinant protein production in bacterial host cell.

The invention also embraces lectomedin variants having additional amino acid residues which result from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of glutathione-S-transferase (GST) fusion product provides the desired polypeptide having an additional glycine residue at position -1 after cleavage of the GST component from the desired polypeptide. Variants which result from expression in other vector systems are also contemplated.

Insertional variants also include fusion proteins wherein the amino and/or carboxy termini of the lectomedin polypeptide is fused to another polypeptide. Examples of such fusion proteins are immunogenic polypeptides, proteins with long circulating half life, such as immunoglobulin constant regions, marker proteins (*e.g.*, fluorescent) and proteins or polypeptide that facilitate purification of the desired lectomedin polypeptide, *e.g.* FLAG<sup>®</sup> tags or polyhistidine sequences.

Deletion variants include lectomedin polypeptides wherein one or more amino acid residues are deleted from the lectomedin amino acid sequence. Deletion variants of the invention embrace polypeptide fragments of the sequence set out in SEQ ID NO: 2, 4, 6, or 58 wherein the fragments maintain biological or immunological properties of a lectomedin polypeptide. Fragments comprising at least 5, 10, 15, 20, 25, 30, 35, or 40 consecutive amino acids of SEQ ID NO: 2, 4, 6, or 58 are comprehended by the invention. Preferred polypeptide fragments display antigenic properties unique to or specific for the lectomedin family of polypeptides. Fragments of the invention having the desired biological and immunological properties can be prepared by any of the methods well known and routinely practiced in the art.



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Substitution variants of the invention include lectomedin polypeptides, or fragments thereof, wherein one or more amino acid residues in the lectomedin amino acid sequence are deleted and replaced with another amino acid residue. Variant polypeptides include those wherein conservative substitutions have been introduced by modification of polynucleotides encoding polypeptides of the invention. Amino acids can be classified according to physical properties and contribution to secondary and tertiary protein structure. A conservative substitution is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out in Table A (from WO 97/09433, page 10, published March 13, 1997 (PCT/GB96/02197, filed 9/6/96), immediately below.

**Table A****Conservative Substitutions I**

<u>SIDE CHAIN CHARACTERISTIC</u>	<u>AMINO ACID</u>
Aliphatic	Non-polar
	G A P
	I L V
	Polar - uncharged
	C S T M
	N Q
	Polar - charged
	D E
	K R
Aromatic	H F W Y
Other	N Q D E

Alternatively, conservative amino acids can be grouped as described in Lehninger, [Biochemistry, Second Edition; Worth Publishers, Inc. NY:NY (1975), pp.71-77] as set out in Table B, immediately below.

Table B

## Conservative Substitutions II

5	SIDE CHAIN CHARACTERISTIC	AMINO ACID
	Non-polar (hydrophobic)	
	A. Aliphatic:	A L I V P
	B. Aromatic:	F W
10	C. Sulfur-containing:	M
	D. Borderline:	G
	Uncharged-polar	
	A. Hydroxyl:	S T Y
	B. Amides:	N Q
15	C. Sulfhydryl:	C
	D. Borderline:	G
	Positively Charged (Basic):	K R H
	Negatively Charged (Acidic):	D E

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As still an another alternative, exemplary conservative substitutions are set out in Table C, below.

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The invention further embraces lectomedin products, or fragments thereof, covalently modified or derivatized, *e.g.*, to include one or more water soluble polymer attachments such as polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. Particularly preferred are lectomedin products covalently modified with polyethylene glycol (PEG) subunits. Water soluble polymers may be bonded at specific positions, for example at the amino terminus of the lectomedin products, or randomly attached to one or more side chains of the polypeptide. Additional derivatives include lectomedin species immobilized on a solid support, pin microparticle, or chromatographic resin, as well as lectomedin polypeptides modified to include one or more non-protein labels, tags, or chelating agents.

**Table C**  
**Conservative Substitutions III**

	<u>Original Residue</u>	<u>Exemplary Substitution</u>
5	Ala (A)	Val, Leu, Ile
	Arg (R)	Lys, Gln, Asn
	Asn (N)	Gln, His, Lys, Arg
	Asp (D)	Glu
	Cys (C)	Ser
10	Gln (Q)	Asn
	Glu (E)	Asp
	His (H)	Asn, Gln, Lys, Arg
	Ile (I)	Leu, Val, Met, Ala, Phe,
	Leu (L)	Ile, Val, Met, Ala, Phe
15	Lys (K)	Arg, Gln, Asn
	Met (M)	Leu, Phe, Ile
	Phe (F)	Leu, Val, Ile, Ala
	Pro (P)	Gly
	Ser (S)	Thr
20	Thr (T)	Ser
	Trp (W)	Tyr
	Tyr (Y)	Trp, Phe, Thr, Ser
	Val (V)	Ile, Leu, Met, Phe, Ala

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Also comprehended by the present invention are antibodies (*e.g.*, monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and CDR-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) and other binding proteins specific for lectomedin products or fragments thereof. Preferred antibodies of the invention are human antibodies which are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its

entirety. Antibody fragments, including Fab, Fab', F(ab')<sub>2</sub>, and F<sub>v</sub>, are also provided by the invention. The term "specific for" indicates that the variable regions of the antibodies of the invention recognize and bind lectomedin polypeptides exclusively (*i.e.*, able to distinguish single lectomedin polypeptides from the family of lectomedin polypeptides despite sequence identity, homology, or similarity found in the family of polypeptides), but may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow *et al.* (Eds), Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the lectomedin polypeptides of the invention are also contemplated, provided that the antibodies are first and foremost specific for, as defined above, lectomedin polypeptides. As with antibodies that are specific for full length lectomedin polypeptides, antibodies of the invention that recognize lectomedin fragments are those which can distinguish single and distinct lectomedin polypeptides from the family of lectomedin polypeptides despite inherent sequence identity, homology, or similarity found in the family of proteins. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

Non-human antibodies may be humanized by any methods known in the art. In one method, the non-human complementarity determining regions (CDRs) are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

Antibodies of the invention are useful for, for example, therapeutic purposes (by modulating activity of lectomedin), diagnostic purposes to detect or quantitate lectomedin, as well as purification of lectomedin. Antibodies are particularly useful for detecting and/or quantitating lectomedin expression in cells, tissues, organs and lysates and extracts thereof, as well as fluids, including serum, plasma, cerebrospinal fluid, urine, sputum, peritoneal fluid, pleural fluid, or pulmonary lavage. Kits comprising

an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific.

5 Specific binding proteins can be identified or developed using isolated or recombinant lectomedin products, lectomedin variants, or cells expressing such products. Binding proteins are useful for purifying lectomedin products and detection or quantification of lectomedin products in fluid and tissue samples using known immunological procedures. Binding proteins are also manifestly useful in modulating (*i.e.*, blocking, inhibiting or stimulating) biological activities of lectomedin, especially those  
10 activities involved in signal transduction.

The DNA and amino acid sequence information provided by the present invention also makes possible the systematic analysis of the structure and function of lectomedins. DNA and amino acid sequence information for lectomedin also permits identification of binding partner compounds with which a lectomedin polypeptide or  
15 polynucleotide will interact. Agents that modulate (*i.e.*, increase, decrease, or block) lectomedin activity or expression may be identified by incubating a putative modulator with a lectomedin polypeptide or polynucleotide and determining the effect of the putative modulator on lectomedin activity or expression. The selectivity of a compound that modulates the activity of the lectomedin can be evaluated by comparing its binding activity  
20 to one particular lectomedin to its activity to other lectomedin polypeptides. Cell based methods, such as di-hybrid assays to identify DNAs encoding binding compounds and split hybrid assays to identify inhibitors of lectomedin polypeptide interaction with a known binding polypeptide, as well as *in vitro* methods, including assays wherein a lectomedin polypeptide, lectomedin polynucleotide, or a binding partner are immobilized, and solution  
25 assays are contemplated by the invention.

Selective modulators may include, for example, antibodies and other proteins or peptides which specifically bind to a lectomedin polypeptide or a lectomedin-encoding nucleic acid, oligonucleotides which specifically bind to a lectomedin polypeptide or a lectomedin gene sequence, and other non-peptide compounds (*e.g.*,  
30 isolated or synthetic organic and inorganic molecules) which specifically react with a lectomedin polypeptide or its underlying nucleic acid. Mutant lectomedin polypeptides

which affect the enzymatic activity or cellular localization of the wild-type lectomedin polypeptides are also contemplated by the invention. Presently preferred targets for the development of selective modulators include, for example: (1) regions of the lectomedin polypeptide which contact other proteins, (2) regions that localize the lectomedin polypeptide within a cell, (3) regions of the lectomedin polypeptide which bind substrate, (4) allosteric regulatory binding site(s) of the lectomedin polypeptide, (5) site(s) of the lectomedin polypeptide wherein covalent modification regulates biological activity and (6) regions of the lectomedin polypeptide which are involved in multimerization of lectomedin subunits. Still other selective modulators include those that recognize specific lectomedin encoding and regulatory polynucleotide sequences. Modulators of lectomedin activity may be therapeutically useful in treatment of a wide range of diseases and physiological conditions in which lectomedin activity is known or suspected to be involved.

Lectomedin polypeptides of the invention are amenable to numerous cell based high throughput screening (HTS) assays known in the art, including melanophore assay to investigate receptor-ligand interaction, yeast based assay systems, and mammalian cell expression systems. For a review, see Jayawickreme and Kost, *Curr. Opin. Biotechnol.* 8:629-634 (1997). Automated and miniaturized HTS assays are also comprehended as described, for example, in Houston and Banks, *Curr. Opin. Biotechnol.* 8:734-740 (1997)

There are a number of different libraries used for the identification of small molecule modulators, including, (1) chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random or designed peptides, oligonucleotides or organic molecules.

Chemical libraries consist of structural analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening. Natural product libraries are collections of microorganisms, animals, plants, or marine organisms which are used to create mixtures for screening by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of plants or marine organisms. Natural product libraries include polyketides, non-ribosomal peptides, and variants (non-naturally occurring) variants thereof. For a review, see Science 282:63-68 (1998). Combinatorial libraries are composed of large

numbers of peptides, oligonucleotides or organic compounds as a mixture. They are relatively easy to prepare by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, Curr. Opin. Biotechnol. 8:701-707 (1997).

Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to modulate activity.

The scientific value of the information contributed through the disclosures of DNA and amino acid sequences of the present invention is manifest. As one series of examples, knowledge of the sequence of a cDNA for lectomedin makes possible through use of Southern hybridization or polymerase chain reaction (PCR) the identification of genomic DNA sequences encoding lectomedin and lectomedin expression control regulatory sequences such as promoters, operators, enhancers, repressors, and the like. DNA/DNA hybridization procedures carried out with DNA sequences of the invention under moderately to highly stringent conditions are likewise expected to allow the isolation of DNAs encoding allelic variants of lectomedin; allelic variants are known in the art to include structurally related proteins sharing one or more of the biochemical and/or immunological properties specific to lectomedin. Similarly, non-human species genes encoding proteins homologous to human lectomedin can also be identified by Southern and/or PCR analysis; species homologs of the invention are particularly useful in animal models for the study of lectomedin-related disorders. As an alternative, complementation studies can be useful for identifying other human lectomedin products as well as non-human proteins, and DNAs encoding the proteins, sharing one or more biological properties of lectomedin.

Polynucleotides of the invention are also useful in hybridization assays to detect the capacity of cells to express lectomedin. Polynucleotides of the invention may also be the basis for diagnostic methods useful for identifying a genetic alteration(s) in a lectomedin locus that underlies a disease state or states.

Also made available by the invention are anti-sense polynucleotides which recognize and hybridize to polynucleotides encoding lectomedin. Full length and fragment anti-sense polynucleotides are provided. The worker of ordinary skill will appreciate that fragment antisense molecules of the invention include (i) those which specifically recognize and hybridize to lectomedin RNA (as determined by sequence comparison of DNA encoding lectomedin to DNA encoding other known molecules) as well as (ii) those which recognize and hybridize to RNA encoding variants of the lectomedin family of proteins. Antisense polynucleotides that hybridize to RNA encoding other members of the lectomedin family of proteins are also identifiable through sequence comparison to identify characteristic, or signature, sequences for the family of molecules. Anti-sense polynucleotides are particularly relevant to regulating expression of lectomedin by those cells expressing lectomedin mRNA.

Antisense nucleic acids (preferably 10 to 20 base pair oligonucleotides) capable of specifically binding to lectomedin expression control sequences or lectomedin RNA are introduced into cells (*e.g.*, by a viral vector or colloidal dispersion system such as a liposome). The antisense nucleic acid binds to the lectomedin target nucleotide sequence in the cell and prevents transcription or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. The antisense oligonucleotides may be further modified by poly-L-lysine, transferrin polylysine, or cholesterol moieties at their 5' end.

The invention further contemplates methods to modulate lectomedin expression through use of ribozymes. For a review, see Gibson and Shillitoe, *Mol. Biotech.* 7:125-137 (1997). Ribozyme technology can be utilized to inhibit translation of lectomedin mRNA in a sequence specific manner through (i) the hybridization of a complementary RNA to a target mRNA and (ii) cleavage of the hybridized mRNA through nuclease activity inherent to the complementary strand. Ribozymes can be identified by empirical methods but more preferably are specifically designed based on accessible sites on the target mRNA (Bramlage, *et al.*, *Trends in Biotech* 16:434-438 (1998). Delivery of ribozymes to target cells can be accomplished using either exogenous or endogenous delivery techniques well known and routinely practiced in the art. Exogenous



delivery methods can include use of targeting liposomes or direct local injection. Endogenous methods include use of viral vectors and non-viral plasmids.

Ribozymes can specifically modulate expression of lectomedin when designed to be complementary to regions unique to a polynucleotide encoding lectomedin. "Specifically modulate" therefore is intended to mean that ribozymes of the invention recognizes only a polynucleotide encoding lectomedin. Similarly, ribozymes can be designed to modulate expression of all or some of the lectomedin family of proteins. Ribozymes of this type are designed to recognize polynucleotide sequences conserved in all or some of the polynucleotides which encode the family of proteins.

The invention further embraces methods to modulate transcription of lectomedin through use of oligonucleotide-directed triplet helix formation. For a review, see Lavrovsky, *et al.*, *Biochem. Mol. Med.* 62:11-22 (1997). Triplet helix formation is accomplished using sequence specific oligonucleotides which hybridize to double stranded DNA in the major groove as defined in the Watson-Crick model. Hybridization of a sequence specific oligonucleotide can thereafter modulate activity of DNA-binding proteins, including, for example, transcription factors and polymerases. Preferred target sequences for hybridization include promoter and enhancer regions to permit transcriptional regulation of lectomedin expression.

Oligonucleotides which are capable of triplet helix formation are also useful for site-specific covalent modification of target DNA sequences. Oligonucleotides useful for covalent modification are coupled to various DNA damaging agents as described in Lavrovsky, *et al.* [*supra*].

Mutations in a lectomedin gene that results in loss of normal function of the lectomedin gene product may underlie lectomedin-related human disease states. The invention comprehends gene therapy to restore lectomedin activity would thus be indicated in treating those disease states (for example, various forms of cancer described herein). Delivery of a functional lectomedin gene to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (*e.g.*, adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (*e.g.*, liposomes or chemical treatments). See, for example, Anderson, *Nature*, supplement to vol. 392, no. 6679, pp.25 (1998). For

additional reviews of gene therapy technology see Friedmann, *Science*, 244: 1275-1281 (1989); Verma, *Scientific American*: 68-84 (1990); and Miller, *Nature*, 357: 455-460 (1992). Alternatively, it is contemplated that in other human disease states, preventing the expression of or inhibiting the activity of lectomedin will be useful in treating the disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of lectomedin.

The invention further embraces pharmaceutical compositions comprising a lectomedin polypeptide of the invention, generally in combination with a pharmaceutically acceptable carrier. The pharmaceutical compositions optionally may include pharmaceutically acceptable (*i.e.*, sterile and non-toxic) liquid, semisolid, or solid diluents that serve as pharmaceutical vehicles, excipients, or media. Any diluent known in the art may be used. Exemplary diluents include, but are not limited to, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl- and propylhydroxybenzoate, talc, alginates, starches, lactose, sucrose, dextrose, sorbitol, mannitol, gum acacia, calcium phosphate, mineral oil, cocoa butter, and oil of theobroma.

The pharmaceutical compositions can be packaged in forms convenient for delivery. The compositions can be enclosed within a capsule, sachet, cachet, gelatin, paper, or other container. These delivery forms are preferred when compatible with entry of the immunogenic composition into the recipient organism and, particularly, when the immunogenic composition is being delivered in unit dose form. The dosage units can be packaged, *e.g.*, in tablets, capsules, suppositories or cachets.

The pharmaceutical compositions may be introduced into the subject to be treated by any conventional method including, *e.g.*, by intravenous, intradermal, intramuscular, intramammary, intraperitoneal, intrathecal, intraocular, retrobulbar, intrapulmonary (*e.g.*, aerosolized drug solutions) or subcutaneous injection (including depot administration for long term release); by oral, sublingual, nasal, anal, vaginal, or transdermal delivery; or by surgical implantation, *e.g.*, embedded under the splenic capsule, brain, or in the cornea. The treatment may consist of a single dose or a plurality of doses over a period of time.

When given parenterally, lectomedin product compositions are generally injected in doses ranging from 1  $\mu$ g/kg to 100 mg/kg per day, preferably at doses

ranging from 0.1 mg/kg to 50 mg/kg per day, and more preferably at doses ranging from 1 to 20 mg/kg/day. The lectomedin product composition may be administered by an initial bolus followed by a continuous infusion to maintain therapeutic circulating levels of drug product. Those of ordinary skill in the art will readily optimize effective dosages and administration regimens as determined by good medical practice and the clinical condition of the individual patient. The frequency of dosing will depend on the pharmacokinetic parameters of the agents and the route of administration. The optimal pharmaceutical formulation will be determined by one skilled in the art depending upon the route of administration and desired dosage. See for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712, the disclosure of which is hereby incorporated by reference. Such formulations may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the administered agents. Depending on the route of administration, a suitable dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art without undue experimentation, especially in light of the dosage information and assays disclosed herein, as well as the pharmacokinetic data observed in the human clinical trials discussed above. Appropriate dosages may be ascertained through use of established assays for determining blood levels dosages in conjunction with appropriate dose-response data. The final dosage regimen will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the drug's specific activity, the severity of the damage and the responsiveness of the patient, the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. As studies are conducted, further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

It will be appreciated that the pharmaceutical compositions and treatment methods of the invention may be useful in the fields of human medicine and veterinary medicine. Thus, the subject to be treated may be a mammal, preferably human, or other

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## Isolation and Characterization of Human Lectomedin

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Among the CD97-related sequences identified as corresponding to known proteins were ESTs representing CD97, human EMR1, and murine F4/80. In addition, several ESTs showed statistically significant values for relatedness in the transmembrane region of CD97, but they were not CD97, EMR1, or F4/80. One of the identified ESTs, designated GenBank<sup>®</sup> Accession No: T47902 (SEQ ID NO: 13), was chosen to attempt identification of a full length cDNA. The basis for choosing T47902 was disclosure in GenBank<sup>®</sup> that the EST was derived from a human fetal spleen library.

A library probe was first generated by PCR based on the Genbank sequence of T47902. Primers used to amplify a T47902 sequence are set out in SEQ ID NOs: 14 and 15 below.

5' TGGAGTTTCAGCTGCTATTG

SEQ ID NO: 14

5' TGCCCATCCACAATAGTCTC

SEQ ID NO: 15

Mixed human adult spleen cDNA was prepared by standard methods and ligated into vector pcDNA1.amp (Invitrogen) [Van der Vieren, M. *et al. Immunity* 3:683-690 (1995)]. The resulting plasmid mixture was transformed into *E. coli* and the bacteria were plated onto LB bacterial plates containing carbenicillin (100 ug/ml). Surviving colonies were collected by scraping and plasmid DNA was prepared by the alkaline lysis method. The cDNA mixture was used as a template for PCR in a reaction mixture including 350 ng cDNA, 100 ng each primer (SEQ ID NO. 14 and NO. 15), 200  $\mu$ M each deoxynucleotide triphosphate (adenosine, thymidine, cytidine and guanosine), 10 mM Tris-HCl, pH 8.3 (at 25°C), 50 mM KCl, 1.5 mM MgCl<sub>2</sub>, and 5 units *Taq* polymerase (Perkin Elmer Corp., Foster City, CA). PCR was carried out with an initial denaturation step of seven minutes at 95°C followed by 30 cycles of denaturation for one minute at 95°C, hybridization for one minute at 55°C, and extension two minutes at 74°C. After PCR, 10  $\mu$ l of the reaction was separated on a 1.5% agarose gel and an amplification product of 306 bp was detected following ethidium bromide staining. The 306 bp product was eluted from the gel using GeneClean<sup>®</sup> (BIO101 Inc., Vista CA) according to the manufacturer's suggested protocol and ligated into vector pCR2.1<sup>®</sup> (TA Cloning<sup>®</sup> kit, Invitrogen, Carlsbad, CA). The resulting plasmid preparation was transformed into *E. coli*

and the cells plated as described above. Several colonies were selected for DNA minipreps and the cDNA inserts were sequenced.

The 306 bp insert was excised from the pCR2.1<sup>®</sup> TA Cloning<sup>®</sup> vector by digestion with *EcoRI*. Following digestion, DNA fragments were fractionated on an agarose gel. A band of approximately 306 bp was eluted from the gel and labeled by random priming according to standard procedures. The labeled probe was used to screen the human spleen adult cDNA pcDNA1 library (described above) immobilized on nylon membranes following colony lifts from cells spread on LB/carbenicillin plates.

Two cDNA clones, designated 3.3 and 15.3.1, were obtained and purified. Clone 3.3 included an insert of approximately 4200 bp and clone 15.3.1 contained an insert of approximately 2750 bp. Both clones were sequenced by standard automated methods. The nucleotide sequence for clone 3.3 is set out in SEQ ID NO: 9 and the predicted amino acid encoded is set out in SEQ ID NO: 10. The nucleotide sequence for clone 15.3.1 is set out in SEQ ID NO: 16. It was initially presumed that the two clones represented a single cDNA sequence and, relying predominantly on the larger 3.3 insert, a contiguous cDNA was predicted. Neither insert, however, encoded a complete open reading frame, as evidenced by the fact that an in frame ATG translation start site preceded by a Kozak translation initiator sequence and an in-frame stop codon were not found.

In an attempt to isolate the 5' end of the complete cDNA, RACE PCR was carried out using a human spleen cDNA library (Marathon<sup>™</sup> cDNA, Clontech, La Jolla, CA). Nested primers (SEQ ID NOs: 17 and 18) utilized in the PCR were designed based on the library vector and clone 3.3 sequences.

5' GTGATCCAGCTACAGTTGTGCTCAT

SEQ ID NO: 17

5' CTAATGCTTCACAGAATCTCTCTGGC

SEQ ID NO: 18

Five microliters of cDNA prepared from human spleen RNA or peripheral blood leukocyte RNA was added to separate reactions with 100 ng downstream nested gene specific primer, adapter primer AP1 (Marathon<sup>™</sup> cDNA kit; Clontech Inc., Palo Alto CA), 200  $\mu$ M each deoxynucleotide triphosphate (adenosine, thymidine, cytidine, and guanosine),

10 mM Tris-HCl, pH 8.3 (at 25°C), 50 mM KCl, 1.5 mM MgCl<sub>2</sub>, 5 units *Taq* polymerase. PCR was carried out with an initial denaturation step for two minutes at 94°C, followed by (i) five cycles of 0.05 minutes at 94°C and seven minutes at 74°C, (ii) five cycles of 0.05 minutes at 94°C and seven minutes at 72°C, and (iii) 25 cycles of 0.05 minutes at 94°C and seven minutes at 70°C. Following amplification, the reaction mixture was diluted 1:50, and 5 µl was used in a second amplification reaction including 100 ng upstream internal gene specific primer and adapter primer AP2 (Marathon™ cDNA kit, Clontech) with the same cycling conditions as in the first amplification. Amplification products from the second reaction were separated on a 0.9% agarose gel and a band of approximately 2 kb in the gel was eluted for subcloning into vector pCR2.1<sup>®</sup> as above. The isolated fragment was designated RACE3.3. The nucleotide and predicted amino acid sequences for the fragment are set out in SEQ ID NOs: 7 and 8, respectively.

When the RACE3.3 sequence was correlated with the sequence for the spleen clone 3.3 to account for overlap, an open reading frame (SEQ ID NO: 33) was deduced encoding a polypeptide of 1114 amino acids (SEQ ID NO: 34) and a predicted molecular weight of approximately 125 kD. Even though the EST used to screen the spleen library was selected based on sequence similarity to CD97, the polypeptide encoded by the overlapping clones was presumed to represent a unique family of human proteins, related to, but distinct from, any previously identified in GenBank<sup>®</sup>. The putative extracellular domain in the predicted amino acid sequence did not include EGF domains characteristic of the CD97-like protein family and the amino acid sequence of the transmembrane domain in the predicted protein was only about 45-60% identical to the transmembrane domains of CD97. In addition, the predicted amino acid sequence deduced from the combined RACE3.3 and clone 3.3 open reading frame included potential lectin-binding, olfactomedin-like, and mucin-like extracellular domains not found in CD97. Based on the presence of the extracellular lectin binding-like and olfactomedin-like domains, the polypeptide encoded by the RACE3.3 and clone 3.3 sequences was designated lectomedin-1 $\alpha$ .

A later BLAST search of the GenBank<sup>®</sup> database using the lectomedin-1 $\alpha$  sequence indicated that lectomedin-1 $\alpha$  was related to the rat receptor for  $\alpha$ -latrotoxin

designated latrophilin [Lenianova, *et al.*, *J. Biol. Chem.* 272:21504-21508 (1997)], and the calcium-independent receptor of  $\alpha$ -latrotoxin (CIRL) [Krasnoperov, *supra*]. Both human lectomedin-1 $\alpha$  and rat latrophilin have extracellular lectin binding-like and olfactomedin-like domains, in addition to a seven transmembrane region and a cytoplasmic domain also found in CD97. Lectomedin-1 $\alpha$  also includes a sequence at amino acid residues 809 to 814 (in SEQ ID NO: 2) which is similar to a proposed cleavage site conserved in both CD97 and latrophilin. It is possible that these three proteins are processed by an endoprotease (or related proteases) with similar primary sequence specificity. In view of these similarities, lectomedin-1 $\alpha$  may be related to a human homolog of the rat latrophilin and may participate in stimulation/secretion coupling in presynaptic termini and/or secretory granule release. Expression of lectomedin in cell and tissue types outside the central nervous system (discussed below), however, indicates that lectomedin is functionally distinct from latrophilin.

The overall amino acid sequence of lectomedin-1 $\alpha$  was found to be approximately 80% identical to that of latrophilin, but the amino acid sequence of the latrophilin cytoplasmic domain was unrelated to the predicted cytoplasmic domain of lectomedin-1 $\alpha$ . In addition, the location of the initiating methionine in latrophilin differed from that in the predicted open reading frame of lectomedin-1 $\alpha$ . After further analysis of the lectomedin-1 $\alpha$  polynucleotide sequence, however, a methionine codon in a different reading frame was identified upstream from the originally predicted open reading frame. The location of the upstream methionine codon (with respect to the transmembrane region) more closely corresponded to the position of the latrophilin initiating methionine and the first few amino acids in reading frame with the upstream methionine codon also corresponded to the sequence in latrophilin.

In view of the potential similarity to latrophilin, the polynucleotide sequence encoding the 1114 amino acid lectomedin-1 $\alpha$  open reading frame was again compared to the raw data obtained during automated sequencing of the RACE3.3 cDNA. Further inspection showed that a guanosine nucleotide at position 454 had been entered in SEQ ID NO: 33, but was not present in the raw sequence data. The corrected nucleotide sequence for RACE3.3 (*i.e.*, having the extraneous guanosine nucleotide deleted) together with the sequence of clone 3.3 (SEQ ID NO: 9) showed an open reading



frame encoding 1177 amino acids. The corrected open reading frame began with the newly identified initiating methionine and included the previously identified lectin binding-like, olfactomedin-like, mucin-like, transmembrane and cytoplasmic domains of lectomedin-1 $\alpha$  (SEQ ID NO: 1).

5               Based on sequence homology with known proteins, domains in various regions of the lectomedin-1 $\alpha$  protein were identified. An extracellular region of approximately 831 amino acids showed homology to a previously reported D-galactoside binding lectin binding-like domain [Ozeki, *et al.*, *Biochemistry* 30:2391-2394 (1991)] (lectomedin-1 $\alpha$  amino acids 36 to 131 of SEQ ID NO: 2) and an olfactomedin-like  
10           domain [Yokoe and Anholt, *Proc. Natl. Acad. Sci. (USA)* 90:4655-4659 (1993)] (lectomedin-1 $\alpha$  amino acids 135 to 327 of SEQ ID NO: 2). Three extracellular and three intracellular domains were separated by seven transmembrane domains (amino acids 832 to 1075 of SEQ ID NO: 2) characteristic of G-protein coupled receptors (GPCR) [Kobilka, *et al.*, *Science* 238:650-656 (1987)]. A cytoplasmic region of 102 amino acids  
15           was adjacent the transmembrane region. Based on the observation that lectomedin-1 $\alpha$  contained a region from amino acids 354 to 563 (SEQ ID NO: 2) with many serine and threonine residues (which may be O-glycosylated), as well as many proline residues (which break up alpha helices resulting in an extended structure with many beta turns), a mucin-like domain was identified.

#### **Identification of Additional Lectomedin-1 Species**

20               The sequence for lectomedin-1 $\alpha$  was based on the sequences determined for clone 3.3 and the fragment RACE3.3. A second lectomedin cDNA could also be deduced based on the sequence of the second spleen clone 15.3.1. In comparing the  
25           sequences for clones 3.3 and 15.3.1, it was first noted that the clones were substantially identical throughout both 5' regions, except that an adenosine required at position 1620 of clone 3.3 (SEQ ID NO: 7) was apparently not present in clone 15.3.1. As a result, the reading frame of clone 15.3.1 was shifted in comparison to the reading frame of clone 3.3, and thus, clone 15.3.1 did not encode a protein having the characteristic seven  
30           transmembrane domain found in lectomedin-1 $\alpha$ . When the variant adenosine was inserted into the sequence for clone 15.3.1, the predicted protein sequence was consistent with the

lectomedin-1 $\alpha$  amino acid sequence up to the first amino acid residue in the cytoplasmic domain. This sequence suggested an alternative splice site in the cytoplasmic region of clone 15.3.1 that produced a shorter cDNA comprising a cytoplasmic domain of approximately forty-eight amino acids (as compared to 107 amino acids in the cytoplasmic domain of the lectomedin-1 $\alpha$  cDNA derived solely from clone 3.3 sequences). The lectomedin-1 $\alpha$  cDNA deduced from clone 3.3 also terminated at an alternative poly(A<sup>+</sup>) site 210 nucleotides upstream from the corresponding poly(A<sup>+</sup>) site identified in clone 15.3.1. The differences suggested that clone 15.3.1 represents a second member of the lectomedin family, which was designated lectomedin-1 $\beta$ . A deduced polynucleotide sequence for lectomedin-1 $\beta$  was therefore generated using the overlapping sequence from clone 3.3 (which extended the 5' region of clone 15.3.1) and the RACE3.3 sequence (to provide an appropriate 5' end); the complete predicted cDNA and deduced amino acid sequences for lectomedin-1 $\beta$  are set out in SEQ ID NOs: 3 and 4, respectively.

Characterization of the predicted amino acid sequence for lectomedin-1 $\beta$  provides various domains similar (in both sequence and position) to those identified for lectomedin-1 $\alpha$ . An extracellular region of approximately 831 amino acids is predicted, including a D-galactoside-binding lectin-like domain (amino acids 36 to 131 of SEQ ID NO: 4), an olfactomedin-like domain (amino acids 135 to 327 of SEQ ID NO: 4), and a mucin-like domain (amino acids 354 to 563 of SEQ ID NO: 4). A seven transmembrane domain (amino acids 832 to 1075 of SEQ ID NO: 4) was located adjacent the extracellular domain, and a cytoplasmic region of 48 amino acids (residues 1076 to 1123 of SEQ ID NO: 4) was located adjacent the transmembrane region.

The originally identified EST designated T49702 (SEQ ID NO: 13) was described in GenBank<sup>®</sup> to represent the 5' end of a cDNA clone designated 71509 (SEQ ID NO: 21), and when GenBank<sup>®</sup> was further searched for a DNA sequence representing the 3' end of clone 71509, a second EST designated T47903 (SEQ ID NO: 30) was identified. Clone 71509 (SEQ ID NO: 21) was purchased, sequenced, and compared to the corresponding regions in lectomedin-1 $\alpha$  and lectomedin-1 $\beta$ . The sequence of clone 71509 was identical to portions of the lectomedin-1 $\alpha$  and 1 $\beta$  sequences, but, like the alternative splicing apparent from comparing lectomedin-1 $\alpha$  and lectomedin-1 $\beta$ , yet another alternative splicing event was found based on the sequence of clone 71509.

Specifically, the sequence of clone 71509 was found to lack a 106 bp sequence found in clone 3.3. Clone 15.3.1 also lacked the same 106 bp and an additional 97 bp of 5' upstream DNA. Clone 15.3.1 therefore lacked 203 bp of sequence found in the lectomedin-1 $\alpha$  clone. The 106 bp deletion resulted in a frame shift in the region encoding the cytoplasmic domain, providing a third lectomedin protein. This third alternative lectomedin polynucleotide and predicted amino acid sequence (SEQ ID NO: 5 and 6, respectively) was designated lectomedin-1 $\gamma$ .

As with the other lectomedin polypeptides, lectomedin-1 $\gamma$  is predicted to include (i) an extracellular region of approximately 831 amino acids with a D-galactoside binding lectin-like domain (amino acids 36 to 131 of SEQ ID NO: 6), an olfactomedin-like domain (amino acids 135 to 327 of SEQ ID NO: 6) and a mucin-like domain (amino acids 354 to 563 of SEQ ID NO: 6), (ii) a seven transmembrane region (amino acids 832 to 1075 of SEQ ID NO: 6), and (iii) a cytoplasmic region of 328 amino acids (amino acids 1076 to 1403 of SEQ ID NO: 6).

The sequences at which the three clones diverged showed hallmarks of the canonical 3' exon sequence with the presence of an AG dinucleotide. However, these regions differed from the accepted intron junction sequences which have been found to include highly conserved GT dinucleotides [GENES IV, B. Lewin, Cell Press, Cambridge MA (1992), p. 597]. The identification of these sequences indicated that the clones were derived from alternatively spliced RNAs rather than from incomplete RNA splicing wherein the canonical exon/intron junction sequence (AG/GT) would be expected.

#### **Identification of Lectomedin-2 and Lectomedin-3 Species**

Lectomedin 1 $\alpha$  and rat latrophilin (SEQ ID NO: 19) were used as query sequences in a subsequent BLAST search in an attempt to identify any additional ESTs with sequence homology. Two human ESTs designated AA683020 (SEQ ID NO: 22) and M79057 (SEQ ID NO: 23) were identified as being closely related to both lectomedin-1 $\alpha$  and rat latrophilin. The sequence for EST AA683020 corresponds to the region from nucleotide 3275 to 3643 in the lectomedin-1 $\alpha$  sequence (SEQ ID NO: 22) and the sequence for EST M79057 corresponds to nucleotides 2561 to 2842 in lectomedin-1 $\alpha$ .

The BLAST search results indicated that both ESTs were more closely related to the sequence encoding rat latrophilin than to the nucleotide sequence encoding lectomedin-1 $\alpha$ , further distinguishing lectomedin-1 $\alpha$  from the rat protein and suggesting that the human ESTs may be more closely related to a putative human homolog of rat latrophilin. In view of the apparent relatedness between the human EST sequences and human lectomedin-1 $\alpha$ , however, the AA683020 and M79057 ESTs were determined to represent unique lectomedin-2 and lectomedin-3 species.

In an effort to isolate cDNAs encoding full length lectomedin-2 and lectomedin-3 proteins, primers were designed based on the EST sequences for both lectomedin-2 and lectomedin-3 to amplify probes for library screening. Primers for amplifying a lectomedin-2 sequence were NHlect2.5 (SEQ ID NO: 35) and NHlect2.3 (SEQ ID NO: 36), and primers for the lectomedin-3 sequence were Nhlct.5 (SEQ ID NO: 37) and Nhlct.3 (SEQ ID NO: 38).

NHlect2.5	GGGCCTCACCTGGGCTTTCGGCCTCCTC	SEQ ID NO: 35
NHlect2.3	GGACTGGTGCCCCCACGCGTGTCTCAGCAC	SEQ ID NO: 36
Nhlct.5	CCAACAAGACCCATACCAGCTGTG	SEQ ID NO: 37
Nhlct.3	CTGAGTCTTGTCGATCCCGACC	SEQ ID NO: 38

PCR was carried out using a Clontech human brain Marathon-Ready™ cDNA library as template. Reaction conditions included an initial incubation at 94°C for five minutes, followed by 25 cycles at 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 30 seconds, followed by a final extension step of 72°C for 7 minutes and cooling to 4°C in a Perkin-Elmer GeneAmp® PCR System 9700. The resulting PCR products were gel purified using low melting point agarose (Gibco/BRL) and a QIAGEN® gel extraction kit according to the manufacturer's suggested protocol. The purified amplification products were separately cloned into vector pCRII® with a TA Cloning® kit (Invitrogen), and sequencing was carried out to identify errors associated with PCR.

Probes for cDNA library screening were prepared by purifying *Eco*RI fragments from the pCRII® clones. The lectomedin-2 digestion products provided two

fragments, 274 and 158 bp, and the 274 bp fragment was purified. The lectomedin-3 digestion resulted in a 297 bp *EcoRI* fragment.

A human fetal brain cDNA library in the LAMBDA ZAP<sup>®</sup> II vector was purchased from Stratagene (La Jolla, CA). Approximately 50,000 pfu were plated on  
5 twenty 150 mm LBM agar plates with LE392 *E. coli*. Plates were inverted and incubated at 37°C overnight. The next day, the plates were chilled at 4°C for two hours before preparing filter replicas. Amersham Hybond<sup>®</sup> N<sup>+</sup> nylon transfer membrane filters, with a diameter of 132 mm and a removal rating of 0.45 µm, were used to prepare two replicas of each plate. Filters were soaked in denaturing solution for two minutes, soaked in  
10 neutralizing solution for two minutes, and UV crosslinked in a Stratagene<sup>®</sup> UV Stratalinker 2400. Filters were prehybridized overnight at 65°C with 20 filters in 80 ml of prehybridization solution.

Hybridization probes were prepared by labeling the *EcoRI* fragments with <sup>32</sup>P-dCTP and <sup>32</sup>P-dTTP (800 Ci/mmol each, NEN Life Sciences Products) using a  
15 random priming kit (Boehringer Mannheim GmbH, Germany). The labeled probes were added to 20 ml hybridization solution per 20 filters and hybridization was carried out at 65°C overnight. The filters were washed the next day and air dried before autoradiography at -70°C for one to three days. Once films were developed, positive  
20 plaques were picked and removed to 500 µl of phage diluent buffer including one drop of chloroform. Dilutions of the positive plaques were prepared and plated on 100 mm LBM agar plates.

The plates were screened a second time as described above using 82 mm Amersham Hybond<sup>®</sup> N<sup>+</sup> filters, except that only one set of replica filters was prepared. Positive plaques from the second screening were screened for a third time to ensure that  
25 only positive plaques were picked for the phage rescue.

Positive plaques were prepared using an Exassist<sup>®</sup>/SOLR phage rescue system (Stratagene, La Jolla, CA) according to the manufacturer's suggested protocol. The rescue procedure produced *E. coli* colonies containing the DNA of interest cloned into a pBluescript<sup>®</sup> SK vector with flanking *EcoRI* restriction sites. Plasmid DNA was  
30 purified using the Wizard<sup>®</sup> Plus Miniprep Kit (Promega, Madison, WI) and digested with *EcoRI* to determine relative size.

The resulting purified clones were analyzed by DNA sequencing at both the 5' and 3' ends. Of the positive clones identified by the probe derived from EST M79057, several of the longest isolates were chosen for complete DNA sequence analysis. Two clones (designated 2.1 and 2.4) were found to comprise overlapping DNA sequences totaling 5611 bp including a complete open reading frame encoding 1470 amino acids. Of the clones identified with the AA683020 probe, all comprised sequences identical to clones derived from EST M79057. These results indicated that the AA683020 and M79057 ESTs represented non-overlapping regions from a single mRNA species. The two clones therefore were derived from the same lectomedin-2 gene. The polynucleotide encoding lectomedin-2 is set out in SEQ ID NO: 57, and its amino acid sequence is set out in SEQ ID NO: 58.

The organization of various domains in the predicted polypeptide sequence of lectomedin-2 was related to that in lectomedin-1. The approximately 851 amino acid extracellular domain of lectomedin-2 included a region with homology to the D-galactoside binding lectin-like domain (amino acids 36 to 131 of SEQ ID NO: 57), an olfactomedin-like domain (amino acids 135 to 325 of SEQ ID NO: 57), three extracellular and three intracellular domains separated by seven transmembrane domains (approximately amino acids 852 to 1095 of SEQ ID NO: 57) and a cytoplasmic region (approximately amino acids 1096 to 1470 of SEQ ID NO: 57). The cytoplasmic region of lectomedin-2 was most similar in length and sequence identity to lectomedin-1 $\gamma$ . Comparison of the overall polypeptide sequences of lectomedin-1 $\gamma$  and lectomedin-2 showed 62.5% amino acid identity. Comparison of the overall polypeptide sequences of lectomedin-2 and CIRL showed 97.6% amino acid identity. These comparisons indicated that lectomedin-2 is more closely related by sequence to CIRL than lectomedin-1 $\gamma$ .

A strategy was designed to assemble the overlapping clones 2-1 and 2-4 in the mammalian expression vector pcDNA3 to produce full length lectomedin-2 open reading frame. Two primers (SEQ ID NOs: 61 and 62) were used to amplify a region of cDNA clone 2-1.

30	JD#1	ATATAAGCTTGCTGCCACCATGGCCCGC	SEQ ID NO: 61
	Lecto-3#31	ATGACCCACAGCCCGTTCTC	SEQ IS NO: 62

Primer JD#1 (SEQ ID NO: 61) incorporated a *Hind*III site to facilitate cloning. The resulting 843 bp amplified product was digested with *Hind*III and *Bam*HI and a 535 bp DNA fragment was isolated. The 535 bp fragment from clone 2-1 was ligated with a 1912 bp *Bam*HI/*Sal*I fragment from clone 2-1, a 2904 bp *Sal*I/*Eco*RV DNA fragment from clone 2-4, and pcDNA3 (Invitrogen) previously digested with *Hind*III and *Eco*RV.

#### **Identification of Additional Lectomedin Species**

A BLAST search of the GenBank EST database with lectomedin-1 $\alpha$  or lectomedin-2 as query sequences identified EST sequences identical to lectomedin-1, EST sequences identical to lectomedin-2 and ESTs that were significantly related to but distinct from both known lectomedins. See Table 1. One of these unique lectomedin ESTs (GenBank Acc# R50822) was derived from clone #37438. Clone #37438 was purchased and its DNA sequence completely determined. The polynucleotide sequence for clone #37438 is set out in SEQ ID NO: 59, and the encoded amino acid sequence is set out in SEQ ID NO: 60. The 3' sequence of clone #37438 is comprised of an untranslated region preceded by a predicted coding sequence for a protein with significant amino acid homology to the cytoplasmic domains of lectomedin-1 $\gamma$  and lectomedin-2. The 5' end of the sequence of clone #37438 was unrelated to the lectomedins, but was identical to the nucleotide sequence for a tRNA synthetase. This clone may represent a partially spliced mRNA or it might be a cloning artifact.

The cDNA clone #37438 was used to generate a labeled probe to screen approximately one million clones from a human fetal brain cDNA library by techniques standard in the art. Hybridization was carried out at 43°C in the presence of 45% formamide and filters were washed in 0.1X SSC at 68°C for 90 minutes. Positive clones identified were isolated to homogeneity and partial sequence analysis was carried out with eleven of the clones. The DNA sequence of one clone (#11) was determined to have 3' sequences identical to clone #37438 and 5' sequences within the upstream coding sequences similar to, but distinct from, lectomedin-1 and lectomedin-2.

**Table 1**  
**Additional Lectomedin Species**

5	Lectomedin-4	T10363	(SEQ ID NO: 39),
		R19057	(SEQ ID NO: 40),
	Lectomedin-5	R50822	(SEQ ID NO: 41)
	Lectomedin-6	W03697	(SEQ ID NO: 42)
	Lectomedin-7	H18951	(SEQ ID NO: 43)
10	Lectomedin-8	AA769730	(SEQ ID NO: 44)
	Lectomedin-9	C17798	(SEQ ID NO: 45)
	Lectomedin-10	Z44961	(SEQ ID NO: 46)
	Lectomedin-11	AA369669	(SEQ ID NO: 47)
	Lectomedin-12	AB011122	(SEQ ID NO: 48)

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**Example 2**  
**Recombinant Expression of Lectomedin**

**Lectomedin-1 $\alpha$**

20           A.     Expression vectors encoding lectomedin isoforms were constructed by combining DNA fragments from clone 3.3 and RACE3.3 described above.

              In one approach, both clone 3.3 and RACE3.3 polynucleotides are first modified in the overlapping regions by insertion of a silent mutation to introduce a *SacI* restriction site. PCR is employed using primers (SEQ ID NOs: 25 and 26) to amplify a  
25     5' sequence from the RACE3.3 cDNA template that changes G to C at position 1455 to create the desired restriction site. In amplification of the RACE3.3 fragment, the 5' primer (SEQ ID NO: 26) is designed based on sequences at the ATG start codon; the primer introduces a *Bam*HI restriction site to facilitate cloning and a Kozak consensus start sequence.

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5'-TCTTCAGCTGAGCTCTTCAAAC

SEQ ID NO: 24

5'-GGTTTTGAAGAGCTCAGCTGAAGA

SEQ ID NO: 25



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5'-CAGCAGGGATCCACCATGGTGTCTT-  
CTGGTTGCAGAATGCGAAGTCTGTGG

SEQ ID NO: 26

5'-GACGATGACGCGGCCCGCCTATTAAAGAC-  
TTGTAACCAGCTGCATTTGTCCTTCTC

SEQ ID NO: 27

In amplification of the clone 3.3 DNA with primers set out in SEQ ID NOs: 24 and 27, the 3' primer is based on sequences at the stop site of translation and is designed to introduce a *NotI* restriction site.

The resulting amplification products, a RACE3.3 fragment with a 5' *BamHI* site and a 3' *SacI* site, and a clone 3.3 DNA with a 5' *SacI* site and a 3' *NotI* site, are digested with appropriate enzymes, ligated together, and cloned into the mammalian expression vector pcDNA+3, (Invitrogen, Carlsbad, CA) previously digested with *BamHI* and *NotI*.

B. As an alternative approach, a lectomedin-1 $\alpha$ -encoding DNA is generated using PCR with the 5' primer used to amplify RACE3.3 described above and the 3' primer used to amplify the clone 3.3 DNA also described above.

In the PCR, both RACE3.3 and clone 3.3 DNA are combined with the two primers. After an initial denaturing step, the RACE3.3 and clone 3.3 DNA will anneal across the overlapping regions and the double stranded region will serve as primers in the first extension that produces a complete double stranded lectomedin-1 $\alpha$  DNA. Subsequent amplifications will result from extension from the 5' and 3' primers. The amplification product is then purified, digested with *BamHI* and *NotI*, and inserted into the pcDNA vector previously digested with the same enzymes.

C. In another approach, an expression vector encoding lectomedin-1 $\alpha$  was constructed in a two step procedure. First, PCR was carried out using a *XbaI* fragments of clone 3.3 and primers 3.3.24 (SEQ ID NO: 52) and Lecto 3' express (SEQ ID NO: 27) along with *Taq* polymerase.

CCTACCACAGCTGTGACAATAACTTCTTCAGCTGAGC

SEQ ID NO: 52

A second PCR was carried out using an *EcoRI* fragment of RACE 3.3 as template DNA and primers Lecto 5' express (SEQ ID NO: 26) and Lecto6 (SEQ ID NO: 25) with Vent<sup>®</sup> polymerase (New England Biolabs, Beverly, MA). The two amplification products were purified, denatured, and annealed. Because the two fragments overlap in a region of approximately 100 nucleotides, annealing results in a partially double stranded molecule spanning the entire lectomedin-1 $\alpha$  coding region. Extension with *Taq* polymerase first produces a double stranded lectomedin-1 $\alpha$  coding region. The double stranded molecule was then amplified using primers in SEQ ID NOs: 26 and 27. The SEQ ID NO: 26 primer was designed to introduce a *Bam*HI restriction site, followed by a Kozak consensus start site. The resulting amplification product was digested with *Not*I and *Bam*HI, and the lectomedin-1 $\alpha$  fragment was gel purified. The fragment was ligated into pcDNA3 (Invitrogen, Carlsbad, CA) previously digested with *Bam*HI and *Not*I. Sequence analysis of the resulting plasmid, designated pcDNA3 Lectomedin-1 $\alpha$ #2, indicated that several errors were introduced in the amplification process. The correct lectomedin-1 $\alpha$  coding sequence was constructed from regions of pcDNA3 Lectomedin-1 $\alpha$ #2 without errors ligated to fragments of RACE3.3 and clone 3.3 as follows.

A 166 bp *Hind*III/*Bgl*II fragment from pcDNA3 Lectomedin-1 $\alpha$ #2, a 628 bp *Bgl*II/*Bst*XI fragment from RACE3.3, and a 775 bp *Bst*XI/*Apa*I fragment from pcDNA3 Lectomedin-1 $\alpha$ #2 were ligated in the presence of pBluescript<sup>®</sup> KS+ (pBSKS) (Stratagene) previously digested with *Bst*XI and *Apa*I. The resulting plasmid was designated pBSKSlectoHindIII/*Apa*I#14.

In a another reaction, a 306 bp *Apa*I/*Eco*RI fragment from clone 3.3 and a 2486 bp *Eco*RI/*Eco*RI fragment from clone 3.3 were ligated in the presence of pBSKS previously digested with *Apa*I and *Eco*RI. The resulting plasmid was designated pBSKSlecto1alpha*Eco*RI/*Apa*I#6.

Plasmids pNEF6 and pDEF2 encode promoter regions and a 5' intron from the gene encoding Chinese hamster ovary elongation factor 1, in addition to neomycin (G418) resistance for selection. Construction of pNEF6 and pDEF2 was carried out as follows.

Plasmid pEF1/XN was generated by ligation of an 11 kb *Not*I/*Xba*I fragment from pSK/EF1.12 (WO 98/49289, published November 5, 1998, incorporated

herein by reference), having the *Xba*I site blunt ended with Klenow polymerase, with a 2.22 *Not*I/*Sma*I fragment from pDC31 (WO 98/49289).

Plasmid pNEF3 was generated by ligation of a 4.19 kb *Sal*I/*Nsi*I fragment (the *Nsi*I site blunt ended with Klenow polymerase) from pSKEF1.7 (WO 98/49289) with a 7.96 kb *Sal*I/*Pme*I fragment from pNEF1 (WO 98/49289).

Plasmid pNEF5 was constructed with a 9.2 kb *Asc*I/*Not*I fragment from pNEF3 and an 11 kb *Asc*I/*Not*I fragment from pEX1/XN.

Plasmid pNEF6 was constructed by ligation of a 19.7 kb *Xba*I/*Asp*718 fragment from pNEF5 with a 0.844 kb *Xba*I/*Asp*718 fragment from pRc/CMv (Invitrogen).

A 736 bp *Not*I/*Hind*III fragment (including the intron sequence) was isolated from pDEF2 and combined with a 1571 *Hind*III/*Apa*I fragment (including the Kozak sequence, translation start site, and coding region for amino acids 1 to 515) from pBSKSlectoHindIII/*Apa*I#14, a 3714 bp *Apa*I/*Xba*I fragment (encoding amino acids 516 to 1177 of lectomedin-1 $\alpha$  and including a stop codon and untranslated sequences) from pBSKSlecto1alphaEcoRI/*Apa*I#6, and pNEF6 previously digested with *Xba*I and *Not*I. The resulting plasmid was designated pNEF6Lectomedin1A#3.1.

#### Lectomedin-1 $\beta$ and Lectomedin-1 $\gamma$

Clone 15.3.1 and clone 71509 were separately amplified with primers lecto3.3.10 and 3.3.19.

TCAGACACTCATACTGCTGTG  
CACAGTCCACAACCTTGAC

SEQ ID NO: 49  
SEQ ID NO: 50

The resulting amplification products were digested with *Stu*I and *Nco*I, and a 113 bp fragment from 15.3.1 (lectomedin-1 $\beta$ ) and a 210 bp fragment from 71509 (lectomedin-1 $\gamma$ ) were purified. Each fragment was separately ligated into pBSKSlecto1alphaEcoRI/*Apa*I#6 previously digested with *Stu*I and *Nco*I. The resulting plasmids were designated pBSKSlecto1betaEcoRI/*Apa*I#7 and pBSKSlecto1gammaEcoRI/*Apa*I#6.

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An expression construct was also prepared in parental vector pDC37 encoding a soluble, truncated form of lectomedin-1 as a fusion protein with human immunoglobulin G1 hinge and constant heavy chain regions 2 and 3 [hinge CH2-CH3] sequence [Sadhu, *et al.*, *Cell Adhesion and Commun.* 2:429-440 (1994)]. Plasmid pDC37, encoding human VCAM-1 with human IgG1 hinge-CH2 coding sequences, is a derivative of pDC31 generated by digestion with *SaII*, filled in with Klenow polymerase, and blunt end ligated to eliminate the *SaII* site.

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Primer lecto Sal Ig generated a unique *SaI* site in the amplification product (after codon 811 of lectomedin-1) to permit in-frame ligation to IgG1 coding sequences. The resulting plasmid was designated pDC37Lecto.Ig#7.

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A 736 bp *NotI*/*HindIII* fragment from pDEF2 was ligated with a 1571 bp *HindIII*/*ApaIII* fragment (encoding the Kozak sequence, start site, and amino acids 1 to 515 from lectomedin-1 $\alpha$ ) from pcDNA3 Lectomedin-1a#2, a 1788 bp *ApaI*/*XbaI* fragment (encoding amino acids 516 to 811 from lectomedin-1 fused to IgG sequences) from pDC37Lecto.Ig#7, and pDEF14 previously digested with *NotI* and *XbaI*. The resulting plasmid was designated pDEF14Lecto.Ig#2.

Plasmid pDEF14Lecto.Ig#2 was transfected into DHFR<sup>-</sup> DG44 CHO cells and stably transfected cells were selected.

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### Example 3 Characterization of Recombinant Lectomedin

Characterization of the protein expression level in recombinant cells is carried out using polyclonal antisera (produced as described in Example 8), and functional analysis, with respect to latrotoxin binding (discussed below) and/or release of secretory granule contents, is performed as previously described.

In initial characterization, Chinese hamster ovary (CHO) cells were transfected by standard methods (*i.e.*, calcium phosphate or cationic lipids) with lectomedin-1 $\alpha$  expression construct. After 48 hours incubation, the cells were lysed in PBS containing 1% Triton<sup>®</sup> X-100 and protease inhibitors, and proteins in the detergent soluble fraction were separated by SDS-PAGE. After transfer to nitrocellulose membrane, the blot was incubated with rabbit antiserum immunospecific for lectomedin-1 $\alpha$  (generated against amino acids 432-852 as immunogen). Immunoreactivity was detected using a goat anti-rabbit IgG (conjugated with horseradish peroxidase) followed by chemiluminescence detection and exposure to X-ray film (using a Renaissance<sup>®</sup> detection kit, NEN Life Sciences, Boston, MA).

For functional characterization, secretory cells of the endocrine system are employed which readily accept DNA constructs by transfection. Cell lines useful in functional characterization include, for example, mouse anterior pituitary corticotroph continuous cells (AtT20; ATCC CCL 89), rat pancreatic islet insulinoma continuous cells (RinM5F), or human pituitary somatotroph continuous cells (GH3; ATCC CCL 82.1). After an appropriate amount of time to allow protein synthesis, incubation of the

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transfected cells with alpha-latrotoxin, or another ligand, is followed by detection of stimulated secretion of proteins using enzyme-linked immunosorbant assay or radioimmunoassay (RIA). For example, increased secretion from the exemplified cells lines is accomplished through detection of adrenocorticotrophic hormone (ACTH) release from AtT20 cells, insulin release from RinM5F cells, or growth hormone release from GH3 cells.

In addition, since lectomedin-1 is a G-protein coupled receptor, ligand binding would be expected to trigger intracellular second messenger effector pathway activity changes such as, for example, increased production of cyclic AMP (cAMP) or changes in intracellular calcium concentration. Changes of these types are measured by standard techniques, for example, RIA detection of cAMP or fluorescence detection of calcium binding indicators (*i.e.*, Fura 2).

An exemplary alpha-latrotoxin binding assay has been previously described [Meldolesi, *J. Neurochem.* 38:1559-1569 (1982), Petrenko, *et al.*, *EMBO J*, 9:2023-2027 (1990)]. Cells are transfected with either vector DNA alone (control cells) or a lectomedin 1-encoding expression plasmid (assay cells). Both assay and control cells are homogenized in buffer (120 mM NaCl, 4.7 mM KCl, 1.2 mM each MgSO<sub>4</sub>, K<sub>2</sub>HPO<sub>4</sub>, and CaCl<sub>2</sub>, 20 mM Na<sub>2</sub>HPO<sub>4</sub>-HCl, pH 7.4, and 10 mM glucose) and protein concentrations are determined by standard methods. Known amounts of protein from control or transfected assay cell membranes are spotted on nitrocellulose paper and placed in separate wells of a 24 well dish. The paper is rinsed once with buffer containing 100 mM KCl, 2 mM CaCl<sub>2</sub>, and 20 mM Tris, pH 7.7, and incubated for one hour in the same buffer supplemented to 1.5% (w/v) with bovine serum albumin (BSA) (blocking buffer). Solutions of blocking buffer containing from 0.1 to 1.2 nM of <sup>125</sup>I-labeled alpha-latrotoxin, labeled to a specific activity of 1500 to 2000 Ci/mmol, without or with a large excess (100 nM) of unlabeled toxin are incubated for thirty minutes with the immobilized protein. The paper is rinsed three times with 1 ml of blocking buffer over a 20 minute time period and counts per minute remaining are determined with a gamma counter. Nonspecific binding is determined to be the value of radioactive counts remaining after incubation of labeled toxin in the presence of a large excess of unlabeled toxin. Specific counts are converted to nanomoles of toxin bound per milligram of protein spotted and the data is plotted as

nanomoles bound toxin versus nanomoles free toxin. The data are converted to bound toxin divided by free toxin versus bound toxin to derive a Scatchard plot for number of binding sites (a linear plot being the expected result for a single toxin binding site on the receptor).

5 In additional characterizations, the lectomedin fusion protein Lecto-1Ig (Example 2) was purified using protein A Sepharose<sup>®</sup> (Amersham Pharmacia Biotech, Piscataway, NJ) affinity chromatography and conditioned growth media derived from one of two clones designated G10 and E10. Media was loaded onto the column which was then washed extensively with 50 mM Tris, pH 7.5, 50 mM NaCl. Protein was eluted in  
10 buffer containing 50 mM citric acid, pH 4.0, and 50 mM citric acid, pH 3.0. The majority of the protein eluted in the pH 3.0 buffer. Protein fractions were pooled, neutralized with 1 M Tris, pH 8.0, and dialyzed against PBS. Purified protein was filtered, aliquoted, flash frozen and stored at -70°C.

15 Amino terminal sequencing indicated that the mature amino terminus of the protein was identified as a phenylalanine residue at position 26. This observation indicated that the recombinant protein was recognized and cleaved by a signal peptidase in the CHO cells and that the amino terminus was not blocked.

Size exclusion chromatography suggested a protein with a molecular weight of approximately 650 kDal as compared to the molecular weight determined on  
20 SDS PAGE of approximately 170 kDal. The gel filtration result suggested that four monomers combined to produce the 650 kDal protein.

Treatment of the protein with N-glycosidase F, O-glycosidase, and/or  
25 neurominidase (Boehringer Mannheim) in 10 mM Na<sub>2</sub>HPO<sub>4</sub> (pH 6.8), 5 mM EDTA, 0.25% Triton<sup>®</sup> X-100, 0.5% SDS, and 0.5%  $\beta$ -mercaptoethanol (BME), at 37°C, resulted in reduction of protein molecular weight. After treatment with N-glycosidase F alone, monomeric protein molecular weight was approximately 130 kDal. After treatment with N-glycosidase F, O-glycosidase, and neuraminidase, monomeric protein molecular weight was approximately 125 kDal. These observations suggest that the observed SDS  
30 PAGE molecular weight may be attributable to approximately 40 kDal N-linked carbohydrate and approximately 5 kDal O-linked carbohydrate.

#### Example 4 Ligand Affinity Chromatography

5 In an attempt to isolate a ligand for lectomedin-1, an affinity column was generated with immobilized lectomedin-1. In short, 10 mg of purified sLecto-1Ig was coupled to CNBr-activated Sepharose<sup>®</sup> 4B resin (AmershamPharmacia) according to the manufacturer's suggested protocol. Greater than 96% of the lectomedin protein was coupled to the resin.

10 A detergent extract was prepared from human spleen (3.48 g wet weight). Tissue was homogenized in 15 ml buffer containing 1% Triton<sup>®</sup> X-100, 25 mM Tris, pH 8, 150 mM NaCl, 5 mM iodoacetamide, 5 mM EDTA, 1 mM phenylmethylsulfonyl fluoride (PMSF), and 1 µg/ml pepstatin and aprotinin using a Waring blender. Homogenization was carried out at low speed. The resulting homogenate was cooled on ice for one hour and centrifuged at 100,000 x g for 60 min. The supernatant  
15 (approximately 120 mg total protein) was mixed with the sLecto-1Ig-coupled resin with rotation overnight at 4°C. The resin was drained and washed extensively with 10 mM Tris (pH 8), 150 mM NaCl, and 10 mM Tris (pH 8), 1 M NaCl. Protein was eluted with five bed volumes of 100 mM D-lactose, 10 mM Tris, pH 8.0, 150 mM NaCl. Five equal fractions were collected. The resin was further eluted with four bed volumes of 100 mM  
20 glycine, pH 2.0, and four equal fractions were collected and neutralized with 1 M Tris, pH 8.0. The resin was then neutralized in 10 mM Tris, pH 8.0/150 mM NaCl. Fractions from the resin were analyzed by SDS-PAGE and bands of approximately 95, 71, 55 and 30 kDal were detected.

Fractions with the highest protein yields were spin concentrated  
25 (Ultrafree<sup>®</sup> 10, Millipore, New Bedford, MA) and proteins were separated with 12% SDS-PAGE. Coomassie staining revealed four prominent bands in the lactose eluate of approximately 30-32, 55, 70, and 80-95 kDal. Bands were excised from the gel, rinsed twice in 50:50 acetonitrile:water, and stored at -70°C until sequence analyses were performed. Sequence results indicated that the 30-32 kDal protein was Mac-2 (also called  
30 galectin-3, GenBank<sup>®</sup> Accession No: g106937), the 55 kDal protein was fibrinogen γ A chain (GenBank<sup>®</sup> Accession No: g71827) and the 80-95 kDal protein was immunoglobulin mu chain constant region.



Mac-2 (galectin-3) is synthesized by numerous immune cell populations and epithelia, and is a major non-integrin laminin binding protein [Perillo, *et al.*, *J. Mol. Med.* 76:402-412 (1998)]. Recent observations indicated that Mac-2 was expressed in vessels in early atherosclerotic lesions in association with infiltrating monocytes. Expression was not detected in normal vessels. Expression was also detected in aortic smooth muscle cells in culture, as well as in animals following a hypercholesterolemic feeding regimen and post balloon angioplasty [Arar, *et al.*, *FEBS Letts.* 430:307-311 (1998), Nachtigal, *et al.*, *Am.J.Pathol.* 152:1199-1208 (1998)]. Mac-2 stimulates normal fibroblast proliferation, neural cell adhesion, and neurite outgrowth [Inohjara, *et la.*, *Exp. Cell. Res.* 245:294-302 (1998); Pesheva, *et al.*, *J. Neurosci. Res.* 54:639-654 (1998)].

The binding results from lectomedin affinity chromatography, in view of the art, suggest that secretion of Mac-2 by infiltrating macrophages during atherogenesis and binding to lectomedin-1 expressed on smooth muscle cells of vascular tunica media may be required for smooth muscle proliferation in atherosclerosis. [Ross, *Nature* 362:801-809 (1993)].

Previous work has indicated that circulating components of the thrombolytic pathway, including fibrinogen, are associated with chronic vascular disease (*i.e.*, hypertension, atherosclerosis). Studies showed that circulating fibrinogen levels may be elevated in hypertensive patient populations. These observations suggest a role for lectomedin in various vascular disease states.

#### **Example 5 Northern Analysis**

In an attempt to assess human lectomedin-1 $\alpha$  expression, Northern blot analysis was performed using a commercial multi-tissue blot (Clontech, Palo Alto, CA) with RNA derived from various human tissue sources. The probe used was a 531 bp *Bst*XI fragment derived from the extracellular region of clone 3.3 (bases 1860 to 2350 in SEQ ID NO: 7). Hybridization was carried out in Express-Hyb™ Solution (Clontech) at 68°C for two hours; the final wash was carried out at 68°C in 0.1X SSC for one hour.

Results indicated expression of two predominant transcripts of 6.6 and 7 kb. The highest levels of expression were detected in spleen, prostate, and lung. Lower

signals were in duodenum, placenta, thymus, testis, colonic mucosa, heart, and liver. Lowest levels were found in skeletal muscle, kidney, pancreas, and brain. No signal was observed in ovary and peripheral blood leukocytes.

### Example 6 *In situ* Hybridization

In order to verify results from Northern analysis, *in situ* hybridization was carried out using various human tissue sections.

Probes for *in situ* hybridization analysis were prepared as follows. Clone 3.3 was engineered by PCR to include a *SacI* site near the 5' end of the cDNA by changing a G nucleotide to C at position 1459 of the composite sequence. A 626 bp *SacI/EcoRI* fragment was prepared and subcloned into pBSSK (Stratagene, La Jolla, CA). The resulting plasmid was linearized with either *EcoRI* or *SacI*. The ends of the *SacI* linearized DNA were made blunt by standard procedures using T4 DNA polymerase. Linear DNAs were used to generate <sup>35</sup>S-labeled sense or antisense strand probes for *in situ* hybridization with tissue sections from spleen, lung, prostate, heart, thymus, duodenum.

The results obtained from hybridization experiments were inconclusive due to high background with sense strand control probe.

In another approach to localizing the lectomedin-1 mRNA, two other fragments of the lectomedin-1 cDNA were subcloned into the pBluescript<sup>®</sup> vector. A 1238 bp *BamHI/SacI* fragment of lectomedin-1 $\alpha$  (SEQ ID NO: 1) was subcloned. A representative clone including this fragment was designated as probe BS. A 2855 bp *BamHI/XbaI* fragment of lectomedin-1 $\alpha$  (SEQ ID NO: 1) was subcloned and a representative clone was isolated and designated as probe BX. <sup>35</sup>S-labeled sense and antisense probes from both BS and BX were prepared by methods standard in the art and hybridized with tissue sections from human brain occipital cortex, cerebellum and thalamus; interventricular septum, sino-atrial node and atrium of the heart; small intestine, spleen, lung, prostate, adrenal gland and pancreas.

Specific signals were observed with the antisense BS probe in cardiac myocytes (heart), endocrine secretory cells of the adrenal cortex, occipital cortex neurons and cerebellar purkinje neurons, granule layer neurons and some molecular layer neurons.

The antisense BX probe produced similar patterns except for the presence of specific signals in a subset of secretory cells of the prostate.

**Example 7**  
**Human Lectomedin Chromosomal Localization**

5

10

The contiguous lectomedin-1 $\alpha$  cDNA deduced from combining clone 3.3 and RACE3.3 sequences was used as a query to search the NCBI Sequence-Tagged Sites (STS) database in an attempt to map the chromosomal location of a gene encoding lectomedin-1 $\alpha$ .

Two STSs were identified, designate SHGC-36772 and WI-11936, which were mapped to chromosome 1 by radiation hybrid mapping techniques. The STS WI-11936 mapping has been further refined to chromosome locus 1p31.

15

20

In an effort to identify the chromosomal localization of the gene for lectomedin-2, the full length nucleotide sequence was used to query the GenBank<sup>®</sup> high throughput genomic sequences nucleotide database using the BLAST algorithm. Results indicated that a portion of chromosome 17 had identity with a portion of the lectomedin-2 DNA sequence. Query of the human Genemap '98 at NCBI for the localization of this region of chromosome 17, showed that the lectomedin-2 gene mapped to chromosome 17p11.1-q12.

25

To identify the chromosomal localization of the gene for lectomedin-3, an accession number query (using EST R50822) of the Unigene database at the National Center for Biotechnology Information (NCBI) was carried out. The results identified a cluster of ESTs, including R50822 that mapped to human chromosome 4. Refinement of the localization was carried by searching the human GeneMap '98 out at NCBI, which showed that EST the cluster containing R80522 was assigned to 4q12-13.3.

### **Generation of Polyclonal Anti-sera With Extracellular Lectomedin-1 Fragments**

PCR primers "lecto-1" and "lecto-2" (SEQ ID NOs: 31 and 32, respectively) were used to amplify a 1283 bp fragment of clone 3.3 (nucleotides 1508-2772 in SEQ ID NO: 9 which encodes the amino acid sequence from residue 432 to residue 852 of SEQ ID NO: 10). This region of the lectomedin-1 polypeptide is approximately 69% identical with latrophilin.

primer lecto-2 SEQ ID NO: 32  
5'-TACAAGATCTAGCAGATAGCCAGGCAAACAAGGG

The plasmid Biolecto1stECD was transformed into *E. coli* using standard procedures and single colonies were isolated and grown for plasmid preparation. A

5 culture including the desired plasmid was grown at 30°C in LB/carbenicillin supplemented with biotin (4 µM) and induced in the presence of arabinose (0.5%) for 16 hours. Bacteria were collected by centrifugation and lysed with hen egg lysozyme (10 µg/ml) in TEN buffer (50 mM Tris-HCl, pH 7.5 at 25°C, 0.5 mM EDTA, 0.3 M NaCl) on ice for 15 minutes. After incubation on ice, NP-40 detergent was added to 0.2% final concentration and the resulting mixture sonicated briefly on ice. Insoluble material was removed by centrifugation at 15,000 x g for ten minutes, after which the pellet washed five times with the additional of TEN buffer followed by sonication and centrifugation. The final pellet was solubilized in 2X sample loading buffer for preparative SDS-PAGE separation.

10 A major band of 55 kDa was detected after treating the gel for 30 minutes in 0.4 M KCl. The 55 kDa band was excised from the gel and the fusion protein eluted in dialysis tubing using 0.5% SDS-PAGE running buffer. The collected protein was concentrated, spin-dialyzed (30,000 MW cutoff Ultrafree<sup>®</sup> Centrifugal Filter Device; Millipore Corp. Bedford, MA), and stored.

15 The purified protein was used to immunize two rabbits to generate antisera according to well known procedures. Briefly, two New Zealand white rabbits (designated #7234 and #7278) were prebled to obtain preimmune serum and then immunized with 250 µg of purified Biolecto1stECD fusion protein emulsified with complete Freund's adjuvant. 20 The rabbits were boosted repeatedly with 250 µg of purified fusion protein in incomplete Freund's adjuvant. The first three boosts were given at one month intervals, the third and fourth boosts following a three month interval, and the fourth and fifth boost following an additional one month interval. Blood was drawn by ear vein puncture two weeks after the second, third, fourth, and fifth boosts to determine antibody titers.

25 Immunoprecipitation was carried out with the resulting polyclonal sera using extracts from tissues/cell lines, including brain cortex, lung, spleen, liver, skeletal muscle, hippocampus, and prostate carcinoma cell line PC-3 (ATCC, CRL 1435). Protein species having molecular weights of 200, 180, 170, and 70 kDa were detected which may have represented full length proteins, proteolytic fragments, or isoforms of lectomedin 30 including the α, β, and γ proteins.

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Serum obtained from rabbit #7234 after the fifth boost was subjected to antigen-specific affinity chromatography by methods standard in the art. Briefly, 10 ml of 0.45 or 0.8 microfiltered serum (100 x g supernatant) adjusted to 10 mM Tris, pH 7.5, was incubated with sLecto-1Ig agarose beads for 16 hours at 4°C with rotation. The beads were drained and washed with 20 bed volumes of 0.5 M NaCl, 10 mM Tris, pH 7.5, until absorbance OD<sub>280</sub> reached 0.03. Bound antibody was eluted with five bed volumes of 100 mM glycine, pH 2.5. The eluates were collected as 0.5 ml fractions and neutralized with 1 M Tris, pH 8. The sLecto-1Ig agarose beads were neutralized with 50 mM Tris, pH 7.5/150 mM NaCl and stored at 4°C in the same buffer supplemented with 0.1% timerool. Fractions were analyzed by SDS-PAGE for the presence of immunoglobulin heavy and light chains. The peak fractions were pooled, the buffer was exchanged with PBS, and the volume reduced by 90%. The final product was mixed with an equal volume of sterile glycerol, aliquoted, flash frozen, and stored at -70°C. until use.

#### 15 **Generation of Polyclonal Antisera With Synthetic Lectomedin-1 Cytoplasmic Peptides**

Peptides specific to the carboxy terminal cytoplasmic regions of  $\alpha$ ,  $\beta$ , and  $\gamma$  isoforms of lectomedin-1 were synthesized as immunogens for producing polyclonal antisera in New Zealand White rabbits. The peptides were designed from the DNA sequence in the cytoplasmic region of lectomedin 1 $\alpha$  (SEQ ID NO: 53), lectomedin 1 $\beta$  (SEQ ID NO: 54), and lectomedin 1 $\gamma$  (SEQ ID NO: 55).

Cys-Leu-Gln-Asp-Leu-Tyr-His-Leu-Glu-Leu-Leu-Leu-Gly-Gln-Ile-Ala  
25 SEQ ID NO: 53

Cys-Thr-Arg-Thr-Ser-Ala-Arg-Tyr-Ser-Ser-Gyl-Thr-Gln-Asp-Ile-His  
SEQ ID NO: 54

Cys-Glu-Gly-Asp-Val-Arg-Glu-Gly-Gln-Met-Gln-Leu-Val-Thr-Ser-Leu  
30 SEQ ID NO: 55

Peptides comprising the carboxy terminal regions of the related lectomedin-2 (SEQ ID NO: 63) and lectomedin-3 (SEQ ID NO: 64) proteins were also synthesized.

Cys-Pro-Gly-Pro-Asp-Gly-Asp-Gly-Gln-Met-Gln-Leu-Val-Thr-Ser-Leu

5

SEQ ID NO: 63

Cys-Pro-Glu-Gly-Ser-Ser-Lys-Gly-Pro-Ala-His-Leu-Val-Thr-Ser-Leu

SEQ ID NO: 64

10 The synthesized peptides were individually conjugated to Keyhole Limpet Hemocyanin (KLH) (Imject, Pierce) according to the manufacturer's suggested protocol. Rabbits were prebled, and 100  $\mu$ g of conjugated peptide in complete Freund's adjuvant was injected per rabbit, two rabbits per isoform. At three week intervals, the rabbits were boosted with the same dose of antigen in incomplete Freud's adjuvant. Animals were bled 10 days after  
15 the third injection and serum titer determined by ELISA.

Briefly, Immulon<sup>®</sup> 4 (Dynax Technologies, Chantilly, VA) plates were coated with unconjugated peptide at 2  $\mu$ g/ml. Plates were blocked with 0.5% fish skin gelatin and washed. Serial dilutions of the pre-immune serum and test bleeds from each rabbit were incubated on the peptide-coated plates. After washing, goat anti-rabbit-horseradish peroxidase (HRP) conjugated secondary antibody was added. The plates  
20 were washed and signal detected by tetramethyl benzidine (TMB) (Sigma) reagent.

Serum from rabbits #6484 and #6453 immunized with the lectomedin-1 $\beta$  peptide showed reactivity three-fold greater than pre-immune serum at a 3000-fold dilution. Serum from rabbits #6868 and #6307 immunized with lectomedin-1 $\gamma$  showed  
25 three-fold greater reactivity over pre-immune serum at a 3000-fold dilution. Serum from rabbits #7347 and #6490 immunized with lectomedin-1 $\alpha$ , showed three-fold greater reactivity at a 200-fold dilution.

In view of these results, a second lectomedin-1 $\alpha$  peptide (SEQ ID NO: 56) was synthesized and the immunization protocol described above was repeated with two  
30 additional rabbits. Serum from these rabbits is assayed for specific reactivity as described above.

Cys-Ser-Arg-Ile-Arg-Arg-Met-Trp-Asn-Asp-Thr-Val-Arg-Lys-Gln-Ser

SEQ ID NO: 56

### **Monoclonal Antibody Production**

5                   In an attempt to produce monoclonal antibodies immunospecific for lectomedin polypeptides, the following procedure was carried out.

                  Five 6 to 12 week old BALB/c mice were prebled on day 0 and immunized by subcutaneous injection with 20 µg of the lectomedin-1α, lectomedin-1β, or lectomedin-1γ peptides (SEQ ID NOs: 53, 54, and 55) described above (60 µg total) in complete Freund's adjuvant. On Days 21, 41, and 62, each mouse was boosted with 10 µg of each peptide (30 µg total) in incomplete Freund's adjuvant. Test bleeds were drawn on day 72 and reactivity determined by ELISA against individual peptides as described in generation of polyclonal antisera, with the exception that specific mouse antibody was detected with a goat anti-mouse-HRP.

15                   Immune serum from all five mice showed reactivity to lectomedin-1β and lectomedin-1γ peptides greater than pre-immune serum at a 12800-fold dilution. Serum from all of the mice showed modest reactivity to lectomedin-1α peptide.

                  Additional peptides comprising the carboxyl termini of lectomedin-2 and lectomedin-3 (SEQ ID NOs: 58 and ) were synthesized to screen for cross reactive antibodies recognizing similar epitopes found in termini of lectomedin-1γ, lectomedin-2 and lectomedin-3.

                  In an another approach to generate an immune response to lectomedin-1α, five additional mice were immunized with the second lectomedin-1α peptide (SEQ ID NO: 56) described above. Immune serum from each of the mice is tested for lectomedin-1α reactivity by ELISA (described above) prior to fusion and hybridoma cloning.

25                   The spleen of the immunized animal is removed aseptically and a single-cell suspension is formed by grinding the spleen between the frosted ends of two glass microscope slides submerged in serum free RPMI 1640 (Gibco, Canada) supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin, and 100 µg/ml streptomycin. The cell suspension is filtered with a sterile 70-mesh Nitex cell strainer (Becton Dickinson, Parsippany, New Jersey), and washed twice by centrifuging at 200 x



g for five minutes and resuspending the pellet in 20 ml serum free RPMI. Thymocytes taken from naive Balb/c mice are prepared in the same manner.

Approximately  $2 \times 10^8$  spleen cells are combined with  $4 \times 10^7$  NS-1 cells (kept in log phase in RPMI with 11% fetal bovine serum [FBS] for three days prior to fusion). The cells are collected by centrifugation and the supernatant is aspirated. The cell pellet is dislodged and 2 ml of 37°C PEG 1500 (50% in 75 mM HEPES, pH 8.0) (Boehringer Mannheim) is added while stirring over the course of one minute, followed by the addition of 14 ml of serum free RPMI over seven minutes. Additional RPMI can be added and the cells are centrifuged at  $200 \times g$  for 10 minutes. After discarding the supernatant, the pellet is resuspended in 200 ml RPMI containing 15% FBS, 100 mM sodium hypoxanthine, 0.4 mM aminopterin, 16 mM thymidine (HAT) (Gibco), 25 units/ml IL-6 (Boehringer Mannheim), and  $1.5 \times 10^6$  thymocytes/ml. The suspension is dispensed into ten 96-well flat bottom tissue culture plates (Corning, United Kingdom) at 200  $\mu$ l/well. Cells are fed on days 2, 4, and 6 days post-fusion by aspirating 100  $\mu$ l from each well and adding 100  $\mu$ l/well plating medium containing 10 U/ml IL-6 and lacking thymocytes.

When cell growth reaches 60-80% confluence (day 8 to 10), culture supernatants are taken from each well and screened for reactivity to lectomedin by ELISA. ELISAs are performed as follows. Immulon<sup>®</sup> 4 plates (Dynatech, Cambridge, Massachusetts) are coated at 4°C with 50  $\mu$ l/well with 100 ng/well of immunogen in 50 mM carbonate buffer, pH 9.6. Plates are washed with PBS with 0.05% Tween<sup>®</sup> 20 (PBST) and blocked 30 minutes at 37°C with 0.5% fish skin gelatin. Plates are washed as described above and 50  $\mu$ l culture supernatant is added. After incubation at 37°C for 30 minutes, plates were washed as above, then 50  $\mu$ l of horseradish peroxidase conjugated goat anti-mouse IgG(fc) (Jackson ImmunoResearch, West Grove, Pennsylvania) [diluted 1:10,000 in PBST] is added. Plates are incubated at 37°C for 30 minutes, washed with PBST and 100  $\mu$ l of substrate, consisting of 1 mg/ml TMB (Sigma) and 0.15 ml/ml 30% H<sub>2</sub>O<sub>2</sub> in 100 mM citrate, pH 4.5, is added. The color reaction is stopped with the addition of 50  $\mu$ l of 15% H<sub>2</sub>SO<sub>4</sub>. Absorbance at 450 nm is read on a plate reader (Dynatech).

**Example 9**  
**Immunocytochemistry for Expression of Lectomedin**

Polyclonal antisera generated in rabbit #7234 (and affinity purified) as described above was used to determine lectomedin expression patterns in human and rat tissues. Human tissues were obtained from the National Disease Research Interchange (NDRI, Philadelphia, PA), including human brain (cortex and cerebellum), heart (septum and atrium), prostate, lung, liver, spleen, small intestines, adrenal gland, and artery (renal, pulmonary and subclavian). Aorta was obtained from the Pathological Determinants of Atherosclerosis in Youth (PDAY) Study, Louisiana State University Medical Center. Rat tissue was prepared using procedures well known and routinely practiced in the art.

Frozen tissues were embedded in OCT (Tissue-Tek), sectioned at 6 micron thickness, mounted onto Superfrost<sup>®</sup> Plus (VWR Scientific) slides, and stored at -20°C until the assay was performed. Paraffin-embedded, formalin-fixed tissues were stored at room temperature until the assay was performed. Prior to assay, frozen tissue was fixed in acetone for two minutes at 4°C, except for brain tissue which was fixed in ether for five minutes at room temperature. Formalin-fixed tissue was deparaffinized with two three-minute washes in each of xylene, 100% ethanol, 95% ethanol, and 70% ethanol. Endogenous peroxidase activity was quenched by incubating the fixed cryosections in buffer containing 0.1% sodium azide and 0.33% hydrogen peroxide in phosphate buffered saline (PBS) during a 15 minute incubation. All incubations were carried out at room temperature unless otherwise indicated. Slides were rinsed in TBST (20 mM Trizma<sup>®</sup> base [Sigma], 150 mM NaCl, 0.05% Tween<sup>®</sup>, pH 7.2) and blocked in a solution containing 30 % normal human serum albumin (Boston Biomedica), 5% normal goat serum (Harlan), and 2% bovine serum albumin (Sigma) in TBST for 30 minutes. Nonspecific binding was blocked using sequential 15 minute incubations with avidin and biotin blocking solution (SP-2001, Vector Labs, Burlingame CA). Slides were rinsed in TSBT after each incubation. Primary antibody at concentrations ranging from 1 µg/ml to 5 µg/ml was applied to each section for one hour, after which sides were washed in TSBT three times. Biotinylated goat anti-rabbit antibody conjugated to peroxidase (Vector Labs) was diluted 1:200 in blocking solution and applied to the slides for 30 minutes. Slides were washed for five minutes and incubated for 30 minutes with ABC Elite reagent (avidin-biotin-peroxidase kit PK-6100, Vector Labs). Slides were washed

twice for five minutes per wash in TSBT. Substrate solution (DAB substrate kit for peroxidase, Vector Labs) was applied to the slides and the desired color intensity was allowed to develop over approximately five minutes. The reaction was stopped with deionized water, and the slides were counterstained with Gill's hematoxylin (Sigma) solution, rinsed in water, dehydrated in ethanol, and mounted with Cytoseal mounting medium (Stephens Scientific) for light microscopic evaluation.

In human brain cortex, labeling with 7234 sera was detected in a subset of neurons (including large and small pyramidal neurons), granule cells, and smooth muscle cells of the vasculature. Human cerebellum staining with 7234 sera was localized to purkinje neurons and neurons of the granular cell layer. Human heart (septal and atrial sections) showed cardiomyocyte immunoreactivity, most prominently at cardiac myocyte cell junctions transverse to the plane of the contractile apparatus called intercalated disks.

In double label experiments using a commercially available connexin antibody (Zymed, San Francisco, CA), which stains connexin found at the intercalated disks, the previous results were confirmed as results indicated that connexin antibody and 7234 antisera staining co-localized on the intercalated disks.

Sections of human prostate showed weak stromal cell labeling and cytoplasmic skeletal muscle staining. Lung staining was found in cartilage and some bronchial smooth muscle cells, with certain cells staining more strongly than others. The medulla of the adrenal gland showed strong positive staining.

Human liver, spleen, and small intestines exhibited a non-specific pattern of immunoreactivity. Human aorta showed immunoreactivity with 7234 sera in the vessel wall that was primarily located in the tunica intima (luminal muscle layer) and tunica media (intermediate muscle layer). Thoracic aorta, pulmonary artery, and renal artery each showed similar staining patterns. When compared with staining with an antibody to smooth muscle  $\alpha$ -actin (an accepted marker for smooth muscle cells), lectomedin-1 immunoreactivity was found primarily in the same cells (*i.e.*, smooth muscle cells).

Staining in rat tissues with 7234 sera demonstrated similar patterns as observed in human tissues. In brain, some neuronal populations and the smooth muscle of the vasculature were stained. In the heart, disks, cardiomyocytes, and vascular smooth muscle all showed immunoreactivity.

While the present invention has been described in terms of specific embodiments, it is understood that variations and modifications will occur to those skilled in the art. Accordingly, only such limitations as appear in the appended claims should be placed on the invention.

What is claimed is:

1. A purified and isolated human seven transmembrane receptor  
lectomedin polypeptide or a fragment thereof, said polypeptide comprising extracellular  
lectin-binding, olfactomedin-like, and mucin-like domains.

2. The polypeptide according to claim 1 which is a mature lectomedin  
polypeptide.

3. The polypeptide according to claim 1 comprising the amino acid  
sequence set out in SEQ ID NO: 2 or a fragment thereof.

4. The polypeptide according to claim 1 comprising the amino acid  
sequence set out in SEQ ID NO: 4 or fragment thereof.

5. The polypeptide according to claim 1 comprising the amino acid  
sequence set out in SEQ ID NO: 6 or fragment thereof.

6. The polynucleotide according to claim 1 comprising the amino acid  
sequence set out in SEQ ID NO: 58 or fragment thereof.

7. A polynucleotide encoding the polypeptide according to any one  
of claims 1 through 6.

8. The polynucleotide according to claim 7 comprising the sequence  
set forth in SEQ ID NO: 1.

9. The polynucleotide according to claim 7 comprising the sequence  
set forth in SEQ ID NO: 3.

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10. The polynucleotide according to claim 7 comprising the sequence set forth in SEQ ID NO: 5.

11. The polynucleotide according to claim 7 comprising the sequence set forth in SEQ ID NO: 57.

12. A polynucleotide encoding a human lectomedin polypeptide selected from the group consisting of:

- a) the polynucleotide according to claim 8 through 11;
- b) a DNA which hybridizes under moderately stringent conditions to the non-coding strand of the polynucleotide of (a); and
- c) a DNA which would hybridize to the non-coding strand of the polynucleotide of (a) but for the redundancy of the genetic code.

13. The polynucleotide of claim 12 which is a DNA molecule.

14. The DNA of claim 13 which is a cDNA molecule.

15. The DNA of claim 13 which is a wholly or partially chemically synthesized DNA molecule.

16. An anti-sense polynucleotide which specifically hybridizes with the polynucleotide of claim 13.

17. A expression construct comprising the polynucleotide according to claim 12.

18. A host cell transformed or transfected with the polynucleotide according to claim 17.

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19. The polynucleotide according to claim 12 operably linked to a heterologous promoter.

20. A host cell comprising the polynucleotide according to claim 19.

21. A method for producing a human lectomedin polypeptide comprising the steps of:

a) growing the host cell according to claim 18 or 20 under conditions appropriate for expression of the lectomedin polypeptide and

b) isolating the lectomedin polypeptide from the host cell or the medium of its growth.

22. An antibody specifically immunoreactive with the polypeptide according to any one of claims 1 through 6.

23. The antibody according to claim 22 which is a monoclonal antibody.

24. A hybridoma which produces the antibody according to claim 23.

25. An anti-idiotypic antibody specifically immunoreactive with the antibody according to claim 23.

26. A method to identify a specific binding partner compound of the lectomedin polypeptide according to any one of claims 1 through 6 comprising the steps of:

a) contacting the lectomedin polypeptide with a compound under conditions which permit binding between the compound and the lectomedin polypeptide;

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- b) detecting binding of the compound to the lectomedin polypeptide; and
- c) identifying the compound as a specific binding partner of the lectomedin polypeptide.

5

27. The method according to claim 26 wherein the specific binding partner modulates activity of the lectomedin polypeptide.

10 28. The method according to claim 27 wherein the compound inhibits activity of the lectomedin polypeptide.

29. The method according to claim 27 wherein the compound enhances activity of the lectomedin polypeptide.

15 30. A method to identify a specific binding partner compound of the lectomedin polynucleotide according to claim 12 comprising the steps of:

- a) contacting the lectomedin polynucleotide with a compound under conditions which permit binding between the compound and the lectomedin polynucleotide;
- 20 b) detecting binding of the compound to the lectomedin polynucleotide; and
- c) identifying the compound as a specific binding partner of the lectomedin polynucleotide.

25 31. The method according to claim 30 wherein the specific binding partner modulates expression of a lectomedin polypeptide encoded by the lectomedin polynucleotide.

30 32. The method according to claim 31 wherein the compound inhibits expression of the lectomedin polypeptide.



33. The method according to claim 31 wherein the compound enhances expression of the lectomedin polypeptide.

34. A compound identified by the method according to claim 26 or 30.

35. A composition comprising the compound according to claim 34 and a pharmaceutically acceptable carrier.

## SEQUENCE LISTING

&lt;110&gt; Hayflick, Joel

&lt;120&gt; Lectomedin Materials and Methods

&lt;130&gt; 27866/35307

&lt;140&gt;

&lt;141&gt;

&lt;150&gt; 60/076,782

&lt;151&gt; 1998-03-04

&lt;160&gt; 64

&lt;170&gt; PatentIn Ver. 2.0

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Ala Asp Lys Ile Tyr Phe Met Pro Trp Thr Pro Tyr Arg Thr Asp Thr	
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Leu Ile Glu Tyr Ala Ser Leu Glu Asp Phe Gln Asn Ser Arg Gln Thr	
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Ile Tyr Asn Thr Arg Leu Asn Arg Gly Glu Tyr Val Asp Val Pro Phe				
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Pro Asn Gln Tyr Gln Tyr Ile Ala Ala Val Asp Tyr Asn Pro Arg Asp				
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Asn Gln Leu Tyr Val Trp Asn Asn Asn Phe Ile Leu Arg Tyr Ser Leu				
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Ile Thr Ser Ser Ala Glu Leu Phe Lys Thr Ile Ile Ser Thr Thr Ser				
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 Asp Tyr Asn Pro Arg Asp Asn Gln Leu Tyr Val Trp Asn Asn Asn Phe  
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 Pro Thr Thr Ala Val Thr Ile Thr Ser Ser Ala Glu Leu Phe Lys Thr  
 405 410 415  
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 Thr Val Ala Gly Ser Gln Glu Gly Ser Lys Gly Thr Lys Pro Pro Pro  
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 Ala Val Ser Thr Thr Lys Ile Pro Pro Ile Thr Asn Ile Phe Pro Leu  
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 Pro Glu Arg Phe Cys Glu Ala Leu Asp Ser Lys Gly Ile Lys Trp Pro  
 465 470 475 480  
 Gln Thr Gln Arg Gly Met Met Val Glu Arg Pro Cys Pro Lys Gly Thr  
 485 490 495  
 Arg Gly Thr Ala Ser Tyr Leu Cys Met Ile Ser Thr Gly Thr Trp Asn  
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 Pro Lys Gly Pro Asp Leu Ser Asn Cys Thr Ser His Trp Val Asn Gln  
 515 520 525  
 Leu Ala Gln Lys Ile Arg Ser Gly Glu Asn Ala Ala Ser Leu Ala Asn  
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 Glu Leu Ala Lys His Thr Lys Gly Pro Val Phe Ala Gly Asp Val Ser  
 545 550 555 560  
 Ser Ser Val Arg Leu Met Glu Gln Leu Val Asp Ile Leu Asp Ala Gln  
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 580 585 590  
 Asn Lys Ala Ile Val Asp Thr Val Asp Asn Leu Leu Arg Pro Glu Ala  
 595 600 605

Leu Glu Ser Trp Lys His Met Asn Ser Ser Glu Gln Ala His Thr Ala  
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 Thr Met Leu Leu Asp Thr Leu Glu Glu Gly Ala Phe Val Leu Ala Asp  
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 Leu Leu Thr Val Ile Thr Trp Val Gly Ile Val Ile Ser Leu Val Cys  
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 Asp Arg Asn Thr Ile His Lys Asn Leu Cys Ile Asn Leu Phe Ile Ala  
 865 870 875 880  
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 Cys Pro Ile Phe Ala Gly Leu Leu His Phe Phe Phe Leu Ala Ala Phe  
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 Lys Ser Tyr Gly Thr Glu Lys Ala Cys Trp Leu His Val Asp Asn Tyr  
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 Tyr Asn Asp Ser Val Gln Val Val Asp Cys Gly Leu Ser Leu Asn Asp  
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 Thr Ala Phe Glu Lys Met Ile Ile Ser Glu Leu Val His Asn Asn Leu  
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 Arg Gly Ser Ser Lys Thr His Asn Leu Glu Leu Thr Leu Pro Val Lys  
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 Ala Ser Ser Leu Met His Ser Asp Asn Pro Gly Leu Glu Leu His His  
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 Ser Gln Leu Thr Ala Glu Ala Glu Asp His Leu Gln Ser Pro Asn Arg  
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 1315 1320 1325  
 Glu Ser Ser Pro Asp Met Glu Glu Asp Leu Ser Pro Ser Arg Arg Ser  
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 Glu Asn Glu Asp Ile Tyr Tyr Lys Ser Met Pro Asn Leu Gly Ala Gly  
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 His Gln Leu Gln Met Cys Tyr Gln Ile Ser Arg Gly Asn Ser Asp Gly  
 1365 1370 1375  
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 gaagatcaat gatgcagact gatggtcttg atgaagctgg gcatttataa ctagattcat 180  
 taaggaatac aaagaaaata cttaaaggga tcaata atg gtg tct tct ggt tgc 234  
 Met Val Ser Ser Gly Cys  
 1 5  
 aga atg cga agt ctg tgg ttt atc att gta atc agc ttc tta cca aat 282  
 Arg Met Arg Ser Leu Trp Phe Ile Ile Val Ile Ser Phe Leu Pro Asn  
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 aca gaa ggt ttc agc aga gca gct tta cca ttt ggg ctg gtg agg cga 330  
 Thr Glu Gly Phe Ser Arg Ala Ala Leu Pro Phe Gly Leu Val Arg Arg  
 25 30 35  
 gaa tta tcc tgt gaa ggt tat tct ata gat ctg cga tgc ccg ggc agt 378  
 Glu Leu Ser Cys Glu Gly Tyr Ser Ile Asp Leu Arg Cys Pro Gly Ser  
 40 45 50  
 gat gtc atc atg att gag agc gct aac tat ggt cgg acg gat gac aag 426  
 Asp Val Ile Met Ile Glu Ser Ala Asn Tyr Gly Arg Thr Asp Asp Lys  
 55 60 65 70  
 att tgt gat gct gac cca ttt cag atg gag aat aca gac tgc tac etc 474



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Ile Cys Asp Ala Asp Pro Phe Gln Met Glu Asn Thr Asp Cys Tyr Leu
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ccc gat gcc ttc aaa att atg act caa agg tgc aac aat cga aca cag      522
Pro Asp Ala Phe Lys Ile Met Thr Gln Arg Cys Asn Asn Arg Thr Gln
      90                      95                      100
tgt ata gta gtt act ggg tca gat gtg ttt cct gat cca tgt cct gga      570
Cys Ile Val Val Thr Gly Ser Asp Val Phe Pro Asp Pro Cys Pro Gly
      105                      110                      115
aca tac aaa tac ctt gaa gtc caa tat gaa tgt gtc cct tac att ttt      618
Thr Tyr Lys Tyr Leu Glu Val Gln Tyr Glu Cys Val Pro Tyr Ile Phe
      120                      125                      130
gtg tgt cct ggg acc ttg aaa gca att gtg gac tca cca tgt ata tat      666
Val Cys Pro Gly Thr Leu Lys Ala Ile Val Asp Ser Pro Cys Ile Tyr
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gaa gct gaa caa aag gcg ggt gct tgg tgc aag gac cct ctt cag gct      714
Glu Ala Glu Gln Lys Ala Gly Ala Trp Cys Lys Asp Pro Leu Gln Ala
      155                      160                      165
gca gat aaa att tat ttc atg ccc tgg act ccc tat cgt acc gat act      762
Ala Asp Lys Ile Tyr Phe Met Pro Trp Thr Pro Tyr Arg Thr Asp Thr
      170                      175                      180
tta ata gaa tat gct tct tta gaa gat ttc caa aat agt cgc caa aca      810
Leu Ile Glu Tyr Ala Ser Leu Glu Asp Phe Gln Asn Ser Arg Gln Thr
      185                      190                      195
aca aca tat aaa ctt cca aat cga gta gat ggt act gga ttt gtg gtg      858
Thr Thr Tyr Lys Leu Pro Asn Arg Val Asp Gly Thr Gly Phe Val Val
      200                      205                      210
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Tyr Asp Gly Ala Val Phe Phe Asn Lys Glu Arg Thr Arg Asn Ile Val
      215                      220                      225                      230
aaa ttt gac ttg agg act aga att aag agt ggc gag gcc ata att aac      954
Lys Phe Asp Leu Arg Thr Arg Ile Lys Ser Gly Glu Ala Ile Ile Asn
      235                      240                      245
tat gcc aac tac cat gat acc tca cca tac aga tgg gga gga aag act      1002
Tyr Ala Asn Tyr His Asp Thr Ser Pro Tyr Arg Trp Gly Gly Lys Thr
      250                      255                      260
gat atc gac cta gca gtt gat gaa aat ggt tta tgg gtc att tac gcc      1050
Asp Ile Asp Leu Ala Val Asp Glu Asn Gly Leu Trp Val Ile Tyr Ala
      265                      270                      275
act gaa cag aac aat gga atg ata gtt att agc cag ctg aat cca tac      1098
Thr Glu Gln Asn Asn Gly Met Ile Val Ile Ser Gln Leu Asn Pro Tyr
      280                      285                      290
act ctt cga ttt gaa gca acg tgg gag act gta tac gac aaa cgt gcc      1146
Thr Leu Arg Phe Glu Ala Thr Trp Glu Thr Val Tyr Asp Lys Arg Ala
      295                      300                      305                      310
gca tca aat gct ttt atg ata tgc gga gtc ctc tat gtg gtt agg tca      1194
Ala Ser Asn Ala Phe Met Ile Cys Gly Val Leu Tyr Val Val Arg Ser
      315                      320                      325

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ccc aac cag tat cag tat att gct gca gtg gat tac aat cca aga gat 1338  
 Pro Asn Gln Tyr Gln Tyr Ile Ala Ala Val Asp Tyr Asn Pro Arg Asp  
 360 365 370

aac caa ctt tac gtg tgg aac aat aac ttc att tta cga tat tct ctg 1386  
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 375 380 385 390

gag ttt ggt cca cct gat cct gcc caa gtg cct acc aca gct gtg aca 1434  
 Glu Phe Gly Pro Pro Asp Pro Ala Gln Val Pro Thr Thr Ala Val Thr  
 395 400 405

ata act tct tca gct gag ctg ttc aaa acc ata ata tca acc aca agc 1482  
 Ile Thr Ser Ser Ala Glu Leu Phe Lys Thr Ile Ile Ser Thr Thr Ser  
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Phe Gly Leu Val Arg Arg Glu Leu Ser Cys Glu Gly Tyr Ser Ile Asp  
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Leu Arg Cys Pro Gly Ser Asp Val Ile Met Ile Glu Ser Ala Asn Tyr  
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Gly Arg Thr Asp Asp Lys Ile Cys Asp Ala Asp Pro Phe Gln Met Glu  
 65 70 75 80

Asn Thr Asp Cys Tyr Leu Pro Asp Ala Phe Lys Ile Met Thr Gln Arg  
 85 90 95

Cys Asn Asn Arg Thr Gln Cys Ile Val Val Thr Gly Ser Asp Val Phe  
 100 105 110

Pro Asp Pro Cys Pro Gly Thr Tyr Lys Tyr Leu Glu Val Gln Tyr Glu  
 115 120 125

Cys Val Pro Tyr Ile Phe Val Cys Pro Gly Thr Leu Lys Ala Ile Val  
 130 135 140

Asp Ser Pro Cys Ile Tyr Glu Ala Glu Gln Lys Ala Gly Ala Trp Cys  
 145 150 155 160  
 Lys Asp Pro Leu Gln Ala Ala Asp Lys Ile Tyr Phe Met Pro Trp Thr  
 165 170 175  
 Pro Tyr Arg Thr Asp Thr Leu Ile Glu Tyr Ala Ser Leu Glu Asp Phe  
 180 185 190  
 Gln Asn Ser Arg Gln Thr Thr Thr Tyr Lys Leu Pro Asn Arg Val Asp  
 195 200 205  
 Gly Thr Gly Phe Val Val Tyr Asp Gly Ala Val Phe Phe Asn Lys Glu  
 210 215 220  
 Arg Thr Arg Asn Ile Val Lys Phe Asp Leu Arg Thr Arg Ile Lys Ser  
 225 230 235 240  
 Gly Glu Ala Ile Ile Asn Tyr Ala Asn Tyr His Asp Thr Ser Pro Tyr  
 245 250 255  
 Arg Trp Gly Gly Lys Thr Asp Ile Asp Leu Ala Val Asp Glu Asn Gly  
 260 265 270  
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 275 280 285  
 Ser Gln Leu Asn Pro Tyr Thr Leu Arg Phe Glu Ala Thr Trp Glu Thr  
 290 295 300  
 Val Tyr Asp Lys Arg Ala Ala Ser Asn Ala Phe Met Ile Cys Gly Val  
 305 310 315 320  
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 325 330 335  
 Lys Asn Ser Ile Asp Tyr Ile Tyr Asn Thr Arg Leu Asn Arg Gly Glu  
 340 345 350  
 Tyr Val Asp Val Pro Phe Pro Asn Gln Tyr Gln Tyr Ile Ala Ala Val  
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ttc aaa acc ata ata tca acc aca agc act act tca cag aaa ggc ccc   96
Phe Lys Thr Ile Ile Ser Thr Thr Ser Thr Thr Ser Gln Lys Gly Pro
          20             25             30

atg agc aca act gta gct gga tca cag gaa gga agc aaa ggg aca aaa  144
Met Ser Thr Thr Val Ala Gly Ser Gln Glu Gly Ser Lys Gly Thr Lys
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cca cct cca gca gtt tct aca acc aaa att cca cct ata aca aat att  192
Pro Pro Pro Ala Val Ser Thr Thr Lys Ile Pro Pro Ile Thr Asn Ile
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ttt ccc ctg cca gag aga ttc tgt gaa gca tta gac tcc aag ggg ata  240
Phe Pro Leu Pro Glu Arg Phe Cys Glu Ala Leu Asp Ser Lys Gly Ile
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aag tgg cct cag aca caa agg gga atg atg gtt gaa cga cca tgc cct  288
Lys Trp Pro Gln Thr Gln Arg Gly Met Met Val Glu Arg Pro Cys Pro
          85             90             95

aag gga aca aga gga act gcc tca tat ctg tgc atg att tcc act gga  336
Lys Gly Thr Arg Gly Thr Ala Ser Tyr Leu Cys Met Ile Ser Thr Gly
          100             105             110

aca tgg aac cct aag ggc ccc gat ctt agc aac tgt acc tca cac tgg  384
Thr Trp Asn Pro Lys Gly Pro Asp Leu Ser Asn Cys Thr Ser His Trp
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gtg aat cag ctg gct cag aag atc aga agc gga gaa aat gct gct agt  432
Val Asn Gln Leu Ala Gln Lys Ile Arg Ser Gly Glu Asn Ala Ala Ser
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ctt gcc aat gaa ctg gct aaa cat acc aaa ggg cca gtg ttt gct ggg  480
Leu Ala Asn Glu Leu Ala Lys His Thr Lys Gly Pro Val Phe Ala Gly
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gat gta agt tct tca gtg aga ttg atg gag cag ttg gtg gac atc ctt  528
Asp Val Ser Ser Ser Val Arg Leu Met Glu Gln Leu Val Asp Ile Leu
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gat gca cag ctg cag gaa ctg aaa cct agt gaa aaa gat tca gct gga  576
Asp Ala Gln Leu Gln Glu Leu Lys Pro Ser Glu Lys Asp Ser Ala Gly
          180             185             190

cgg agt tat aac aag gca att gtt gac aca gtg gac aac ctt ctg aga  624
Arg Ser Tyr Asn Lys Ala Ile Val Asp Thr Val Asp Asn Leu Leu Arg
          195             200             205

cct gaa gct ttg gaa tca tgg aaa cat atg aat tct tct gaa caa gca  672
Pro Glu Ala Leu Glu Ser Trp Lys His Met Asn Ser Ser Glu Gln Ala
          210             215             220

cat act gca aca atg tta ctg gat aca ttg gaa gaa gga gct ttt gtc  720

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 Leu Ala Asp Asn Leu Leu Glu Pro Thr Arg Val Ser Met Pro Thr Glu  
 245 250 255  
 aat att gtc ctg gaa gtt gcc gta ctc agt aca gaa gga cag atc caa 816  
 Asn Ile Val Leu Glu Val Ala Val Leu Ser Thr Glu Gly Gln Ile Gln  
 260 265 270  
 gac ttt aaa ttt cct ctg ggc atc aaa gga gca ggc agc tca atc caa 864  
 Asp Phe Lys Phe Pro Leu Gly Ile Lys Gly Ala Gly Ser Ser Ile Gln  
 275 280 285  
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 290 295 300  
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 305 310 315 320  
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 325 330 335  
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 Ser Arg Val Tyr Leu Thr Asp Pro Val Leu Phe Thr Leu Pro His Ile  
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 Asp Pro Asp Asn Tyr Phe Asn Ala Asn Cys Ser Phe Trp Asn Tyr Ser  
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 Phe Ala Ile Leu Met Ala His Arg Glu Ile Ala Tyr Lys Asp Gly Val  
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485 490 495	
gcg att gca tgc cca ata ttt gca gga ctt cta cac ttt ttc ttt ttg	1536
Ala Ile Ala Cys Pro Ile Phe Ala Gly Leu Leu His Phe Phe Leu	
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515 520 525	
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Leu Val Glu Val Phe Glu Ser Glu Tyr Ser Arg Lys Lys Tyr Tyr Tyr	
530 535 540	
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Val Ala Gly Tyr Leu Phe Pro Ala Thr Val Val Gly Val Ser Ala Ala	
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Ile Asp Tyr Lys Ser Tyr Gly Thr Glu Lys Ala Cys Trp Leu His Val	
565 570 575	
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Asp Asn Tyr Phe Ile Trp Ser Phe Ile Gly Pro Val Thr Phe Ile Ile	
580 585 590	
ctg cta aat att atc ttc ttg gtg atc aca ttg tgc aaa atg gtg aag	1824
Leu Leu Asn Ile Ile Phe Leu Val Ile Thr Leu Cys Lys Met Val Lys	
595 600 605	
cat tca aac act ttg aaa cca gat tct agc agg ttg gaa aac att aag	1872
His Ser Asn Thr Leu Lys Pro Asp Ser Ser Arg Leu Glu Asn Ile Lys	
610 615 620	
tct tgg gtg ctt ggc gct ttc gct ctt ctg tgt ctt ctt ggc ctc acc	1920
Ser Trp Val Leu Gly Ala Phe Ala Leu Leu Cys Leu Leu Gly Leu Thr	
625 630 635 640	
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Trp Ser Phe Gly Leu Leu Phe Ile Asn Glu Glu Thr Ile Val Met Ala	
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tat ctc ttc act ata ttt aat gct ttc cag gga gtg ttc att ttc atc	2016
Tyr Leu Phe Thr Ile Phe Asn Ala Phe Gln Gly Val Phe Ile Phe Ile	
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Phe His Cys Ala Leu Gln Lys Lys Val Arg Lys Glu Tyr Gly Lys Cys	
675 680 685	
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Ser Ser Val Lys Ala Ser Thr Thr Arg Thr Ser Ala Arg Tyr Ser Ser	
705 710 715 720	
ggc aca cag agt cgt ata aga aga atg tgg aat gat act gtg aga aaa	2208
Gly Thr Gln Ser Arg Ile Arg Arg Met Trp Asn Asp Thr Val Arg Lys	

725	730	735	
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Gln Ser Glu Ser Ser Phe Ile Ser Gly Asp Ile Asn Ser Thr Ser Thr			
740	745	750	
ctt aat caa gga ctg aca tca cat ggt ctg aga gcc cat ctt caa gat			2304
Leu Asn Gln Gly Leu Thr Ser His Gly Leu Arg Ala His Leu Gln Asp			
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Arg Ser Tyr Asn Lys Ala Ile Val Asp Thr Val Asp Asn Leu Leu Arg  
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Pro Glu Ala Leu Glu Ser Trp Lys His Met Asn Ser Ser Glu Gln Ala  
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Cys	Val	Asn	Ala	Thr	Ala	Cys	Arg	Cys	Asn	Pro	Gly	Phe	Ser	Ser	Phe		
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 Trp Ala Val Ala Ala Gly Ala Glu Asp Pro Gly Pro Ala Val Ala Gly  
 385 390 395 400  
 Ile Leu Ser Ile Gln Asn Met Thr Thr Leu Leu Ala Asn Ala Ser Leu  
 405 410 415  
 Asn Leu His Ser Lys Lys Gln Ala Glu Leu Glu Glu Ile Tyr Glu Ser  
 420 425 430

Ser Ile Arg Gly Val Gln Leu Arg Arg Leu Ser Ala Val Asn Ser Ile  
 435 440 445  
 Phe Leu Ser His Asn Asn Thr Lys Glu Leu Asn Ser Pro Ile Leu Phe  
 450 455 460  
 Ala Phe Ser His Leu Glu Ser Ser Asp Gly Glu Ala Gly Arg Asp Pro  
 465 470 475 480  
 Pro Ala Lys Asp Val Met Pro Gly Pro Arg Gln Glu Leu Leu Cys Ala  
 485 490 495  
 Phe Trp Lys Ser Asp Ser Asp Arg Gly Gly His Trp Ala Thr Glu Gly  
 500 505 510  
 Cys Gln Val Leu Gly Ser Lys Asn Gly Ser Thr Thr Cys Gln Cys Ser  
 515 520 525  
 His Leu Ser Ser Phe Ala Ile Leu Met Ala His Tyr Asp Val Glu Asp  
 530 535 540  
 Trp Lys Leu Thr Leu Ile Thr Arg Val Gly Leu Ala Leu Ser Leu Phe  
 545 550 555 560  
 Cys Leu Leu Leu Cys Ile Leu Thr Phe Leu Leu Val Arg Pro Ile Gln  
 565 570 575  
 Gly Ser Arg Thr Thr Ile His Leu His Leu Cys Ile Cys Leu Phe Val  
 580 585 590  
 Gly Ser Thr Ile Phe Leu Ala Gly Ile Glu Asn Glu Gly Gly Gln Val  
 595 600 605  
 Gly Leu Arg Cys Arg Leu Val Ala Gly Leu Leu His Tyr Cys Phe Leu  
 610 615 620  
 Ala Ala Phe Cys Trp Met Ser Leu Glu Gly Leu Glu Leu Tyr Phe Leu  
 625 630 635 640  
 Val Val Arg Val Phe Gln Gly Gln Gly Leu Ser Thr Arg Trp Leu Cys  
 645 650 655  
 Leu Ile Gly Tyr Gly Val Pro Leu Leu Ile Val Gly Val Ser Ala Ala  
 660 665 670  
 Ile Tyr Ser Lys Gly Tyr Gly Arg Pro Arg Tyr Cys Trp Leu Asp Phe  
 675 680 685  
 Glu Gln Gly Phe Leu Trp Ser Phe Leu Gly Pro Val Thr Phe Ile Ile  
 690 695 700  
 Leu Cys Asn Ala Val Ile Phe Val Thr Thr Val Trp Lys Leu Thr Gln  
 705 710 715 720  
 Lys Phe Ser Glu Ile Asn Pro Asp Met Lys Lys Leu Lys Lys Ala Arg  
 725 730 735  
 Ala Leu Thr Ile Thr Ala Ile Ala Gln Leu Phe Leu Leu Gly Cys Thr  
 740 745 750  
 Trp Val Phe Gly Leu Phe Ile Phe Asp Asp Arg Ser Leu Val Leu Thr  
 755 760 765



Tyr Val Phe Thr Ile Leu Asn Cys Leu Gln Gly Ala Phe Leu Tyr Leu  
 770 775 780  
 Leu His Cys Leu Leu Asn Lys Lys Val Arg Glu Glu Tyr Arg Lys Trp  
 785 790 795 800  
 Ala Cys Leu Val Ala Gly Gly Ser Lys Tyr Ser Glu Phe Thr Ser Thr  
 805 810 815  
 Thr Ser Gly Thr Gly His Asn Gln Thr Arg Ala Leu Arg Ala Ser Glu  
 820 825 830  
 Ser Gly Ile  
 835

<210> 13  
 <211> 867  
 <212> DNA  
 <213> Homo sapiens

<400> 13  
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 agctatggaa cagaaaaagc ttgctggcct catgttgata actactttat atggagcttc 120  
 attggacctg ttaccttcat tattctgcta aatattatct tcttggtgat cacattgtgc 180  
 aaaatggtga agcattcaaa cactttgaaa ccagattcta gcaggttgga aaacattaag 240  
 tcttgggggtg cttggcgctt tcgctcttct gtgtcttctt ggctcacct gggtcctttg 300  
 ggggttgcttt ttattaatga gggagactat tgtggatggg catatctctt tcaattatat 360  
 ttaattgctt tccgggggag tgttccattt tccatctttc cactgtgctc tccaaaagga 420  
 agtaatgata tatatcatat atcttgatct cagcttcaaa attgctactt agctaggtat 480  
 atatatagta gaagatttat agtaatcaac tatctcttct ctctagtaa gtactaatcg 540  
 aattcggcac gagaatctc gagttttttt tttttttttt tttatttagt tccataaatt 600  
 aatattctat ttactctatc attaatacaa tgaaagtat aattaaaata taatagttat 660  
 cggcactaaa ttctattgca ggatattcat tgcaggccta tgcaggataa tagcacctat 720  
 gccgcctatg caaggcaagg atgtcctcaa tgaaggagac acgctcctga actcaagggc 780  
 aatgaaggca cgctcgcgca cgctcaggat aactcaggga tagatcaatt aagggtaaat 840  
 cggtaaatca ggctccaaaa gggaaaa 867

<210> 14  
 <211> 20  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: primer

<400> 14

tggagtttca gctgctattg

20

<210> 15

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 15

tgcccatcca caatagtctc

20

<210> 16

<211> 3165

<212> DNA

<213> Homo sapiens

<400> 16

aagaaagagt ccagccgagt atacctgact gatcctgtgc tttttaccct gccacacatt 60  
 gatcctgaca attatttcaa tgcaaactgc tccttctgga actactcaga gagaactatg 120  
 atgggatatt ggtctacca gggtgcaag ctggttgaca ctaataaaac tcgaacaacg 180  
 tgtgcatgca gccacctaac caattttgca attctcatgg cccacagga aattgcatat 240  
 aaagatggcg ttcattgaatt acttcttaca gtcattcacct ggggtgggaat tgcattttcc 300  
 cttgtttgccc tggctatctg catcttcacc ttctgctttt tccgtggcct acagagtgc 360  
 cgaaatacta ttcacaagaa cctttgtatc aaccttttca ttgctgaatt tattttcccta 420  
 ataggcattg ataagacaaa atatgcgatt gcatgcccaa tatttgcagg acttctacac 480  
 tttttctttt tggcagcttt tgcttggatg tgcctagaag gtgtgcagct ctacctaatg 540  
 ttagttgaag tttttgaaag tgaatattca aggaaaaata ttactatgtt gctggttact 600  
 tgtttcctgc cacagtgggt ggagtttcag ctgctattga ctataagagc tatggaacag 660  
 aaaaagcttg ctggcttcat gttgataact acttttatatg gagcttcatt ggacctgtta 720  
 ccttcattat tctgctaaat attatcttct tgggtgatcac attgtgcaaa atggtgaagc 780  
 attcaaacac tttgaaacca gattctagca ggttgaaaa cattaagtct tgggtgcttg 840  
 gcgctttcgc tcttctgtgt cttcttggcc tcacctgggc ctttgggttg ctttttatta 900  
 atgaggagac tattgtgatg gcatatctct tcactatatt taatgctttc cagggagtgt 960  
 tcattttcat ctttctactgt gctctccaaa agaaagtacg aaaagaatat ggcaagtgc 1020  
 tcagacactc atactgctgt ggaggcctcc caactgagag tccccacagt tcagtgaagg 1080  
 catcaaccac cagaaccagt gctcgctatt cctctggcac acaggacatt cactgaacaa 1140  
 tgccagggat acaagtgcc tggatactct accgctaaat ggtaatttta acaacagcta 1200  
 ctgctgcac aagggtgact ataattgacag cgtgcaagtt gtggactgtg gactaagtct 1260

gaatgatact gcttttgaga aaatgatcat ttcagaatta gtgcacaaca acttacgggg 1320  
cagcagcaag actcacaacc tggagctcac gctaccagtc aaacctgtga ttggaggtag 1380  
cagcagtga gatgatgcta ttgtggcaga tgcctcatct ttaatgcaca gcgacaaccc 1440  
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ccttctgtac caaccccaga agaaagtga gtccgaggga actgacagct atgtctccca 1560  
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catgccaat cttagagact ctccctatcc ggagagcagc cctgacatgg aagaagacct 1680  
ctctccctcc agggaggagtg agaattgagga catttactat aaaagcatgc caaatcttgg 1740  
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gctggttaca agtctttaat catcacgcta aggaattcca agggccacat gcgagtatta 1920  
ataaataaag acaccattgg cctgacgcag ctccctcaa ctctgcttga agagatgact 1980  
cttgacctgt ggttctctgg tgtaaaaaag atgactgaac cttgcagttc tgtgaatttt 2040  
tataaaacat acaaaaactt tgtatataca cagagtatac taaagtgaat tatttgttac 2100  
aaagaaaaga gatgccagcc aggtatttta agattctgct gctgtttaga gaaattgtga 2160  
aacaagcaaa acaaaaactt ccagccattt tactgcagca gtctgtgaac taaatttgta 2220  
aatatggctg caccattttt gtaggcctgc attgtattat atacaagacg taggctttta 2280  
aatcctgtgg gacaaattta ctgtacctta ctattcctga caagacttgg aaaagcagga 2340  
gagatattct gcatcagttt gcagttcact gcaaactctt tacattaagg caaagattga 2400  
aaacatgctt aaccactagc aatcaagcca caggccttat ttcatatgtt tcctcaactg 2460  
tacaatgaac tattctcatg aaaaatggct aaagaaatta tattttgttc tattgctagg 2520  
gtaaaataaa tacatttggtg tccaactgaa atataattgt cattaaaata attttaaaga 2580  
gtgaagaaaa tattgtgaaa agctcttgggt tgcacatgtt atgaaatgtt tttcttaca 2640  
ctttgtcatg gtaagttcta ctcatcttca cttcttttcc actgtatata gtgttctgct 2700  
ttgacaaagt tagtctttat tacttacatt taaatttctt attgccaaaa gaacgtgttt 2760  
tatggggaga acaaaactct ttgaagccag ttatgtcatg ccttgacaaa aagtgatga 2820  
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gggcacttct cacaaaactt ctagtgaaca aaaggtgcct attctttttt aaaaaataa 2940  
aataaaacat aatatattact ctccatatt ccttctgcct atatttagta attaatttat 3000  
tttatgataa agttctaag aaatgtaaat tgtttcagca aaattctgct ttttttcat 3060  
ccctttgtgt aaacctgtta ataagagcc catcactaat atccagtgt aagttaaca 3120

cggtttgaca gtaaataaat gtgaattttt tcaaaaaaaaa aaaaa

3165

<210> 17  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: primer

<400> 17  
 gtgatccagc tacagttgtg ctcac

25

<210> 18  
 <211> 26  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: primer

<400> 18  
 ctaatgcttc acagaatctc tctggc

26

<210> 19  
 <211> 5693  
 <212> DNA  
 <213> Rattus rattus

<220>  
 <221> CDS  
 <222> (425)..(4822)

<400> 19  
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 acccgcgccg ccggggccgg ggccgcctcc ggagcgccgc gatccgcctt ttctttcctt 120  
 ttttttcctt tcccttcttc ctttttaaatt tttggttggt ggcggcagtg ctgggcccga 180  
 ggaaagaagg gacacggagt cctccctcgc tcagccaccc cctccccgct tccccctggg 240  
 ccgggctccg ggagatgtgc cgggcggggg gcccggttc gccgagccgc gggaggagcg 300  
 cgcacggccg accccgaagc gccgctggac aggctggttg gccaggcctt ggtaccctgg 360  
 tgatgcgggg caaggcccc cccacagtcc gctgagatca ccgtgccgc cctggcctt 420  
 cgcc atg gcc cgc ttg gct gca gca ctc tgg agt ctc tgt gtg acg act 469  
 Met Ala Arg Leu Ala Ala Ala Leu Trp Ser Leu Cys Val Thr Thr  
 1 5 10 15  
 gtc ctc gtc acc tct gct acc caa ggc ctg agc cgg gct gga ctc cca 517  
 Val Leu Val Thr Ser Ala Thr Gln Gly Leu Ser Arg Ala Gly Leu Pro  
 20 25 30  
 ttt gga ttg atg cgc cgg gag cta gca tgc gaa ggc tac ccc att gag 565  
 Phe Gly Leu Met Arg Arg Glu Leu Ala Cys Glu Gly Tyr Pro Ile Glu  
 35 40 45

ctg cgg tgc ccg ggc agt gac gtc atc atg gtg gag aat gca aac tat	613
Leu Arg Cys Pro Gly Ser Asp Val Ile Met Val Glu Asn Ala Asn Tyr	
50 55 60	
ggg cgc aca gat gac aag atc tgc gat gcc gac cct ttt cag atg gag	661
Gly Arg Thr Asp Asp Lys Ile Cys Asp Ala Asp Pro Phe Gln Met Glu	
65 70 75	
aac gtg cag tgc tac ctg cct gac gcc ttc aaa atc atg tca cag aga	709
Asn Val Gln Cys Tyr Leu Pro Asp Ala Phe Lys Ile Met Ser Gln Arg	
80 85 90 95	
tgt aat aac cga acc cag tgt gtg gtg gtg gcc ggc tct gac gcc ttt	757
Cys Asn Asn Arg Thr Gln Cys Val Val Ala Gly Ser Asp Ala Phe	
100 105 110	
cct gac ccc tgt cct gga acc tac aag tac ctg gag gtg cag tac gac	805
Pro Asp Pro Cys Pro Gly Thr Tyr Lys Tyr Leu Glu Val Gln Tyr Asp	
115 120 125	
tgt gtc cct tac atc ttc gtg tgc cca ggg aca ctg cag aag gtg ctg	853
Cys Val Pro Tyr Ile Phe Val Cys Pro Gly Thr Leu Gln Lys Val Leu	
130 135 140	
gag ccc acc tcc aca cat gaa tgc gag cac cag tct ggc gca tgg tgc	901
Glu Pro Thr Ser Thr His Glu Ser Glu His Gln Ser Gly Ala Trp Cys	
145 150 155	
aag gac cca ctg cag gca ggt gac cgt atc tac gtt atg ccc tgg atc	949
Lys Asp Pro Leu Gln Ala Gly Asp Arg Ile Tyr Val Met Pro Trp Ile	
160 165 170 175	
ccc tac cgc acg gac aca ctg acc gag tat gct tcc tgg gag gac tat	997
Pro Tyr Arg Thr Asp Thr Leu Thr Glu Tyr Ala Ser Trp Glu Asp Tyr	
180 185 190	
gtg gct gca cgc cac acc acc acg tac aga ctg ccc aac cgt gta gat	1045
Val Ala Ala Arg His Thr Thr Thr Tyr Arg Leu Pro Asn Arg Val Asp	
195 200 205	
ggc act ggc ttt gtg gta tat gat ggt gcc gtc ttc tat aac aag gaa	1093
Gly Thr Gly Phe Val Val Tyr Asp Gly Ala Val Phe Tyr Asn Lys Glu	
210 215 220	
cgt act cgc aac att gtc aaa tat gac ctg cgg acc cgc atc aag agc	1141
Arg Thr Arg Asn Ile Val Lys Tyr Asp Leu Arg Thr Arg Ile Lys Ser	
225 230 235	
gga gaa aca gtc ata aac aca gcc aac tac cac gac acc tca cct tat	1189
Gly Glu Thr Val Ile Asn Thr Ala Asn Tyr His Asp Thr Ser Pro Tyr	
240 245 250 255	
cgc tgg gga ggc aaa acc gac att gac ctg gca gtg gat gag aac ggg	1237
Arg Trp Gly Gly Lys Thr Asp Ile Asp Leu Ala Val Asp Glu Asn Gly	
260 265 270	
ctg tgg gtc atc tat gcc acc gag ggg aac aac ggg cgt ctg gtg gtg	1285
Leu Trp Val Ile Tyr Ala Thr Glu Gly Asn Asn Gly Arg Leu Val Val	
275 280 285	
agc cag ctc aac ccc tac aca ctg cgt ttc gag ggc acc tgg gaa aca	1333
Ser Gln Leu Asn Pro Tyr Thr Leu Arg Phe Glu Gly Thr Trp Glu Thr	

290	295	300	
ggc tat gac aag cgc tca gcc tcc aat gcc ttc atg gtg tgt ggt gtc Gly Tyr Asp Lys Arg Ser Ala Ser Asn Ala Phe Met Val Cys Gly Val 305 310 315			1381
ctc tat gtg ctg cgc tct gtt tat gtg gat gac gac agt gag gca gca Leu Tyr Val Leu Arg Ser Val Tyr Val Asp Asp Asp Ser Glu Ala Ala 320 325 330 335			1429
ggc aac cgc gtg gac tat gcc ttt aac acc aat gca aac cga gag gag Gly Asn Arg Val Asp Tyr Ala Phe Asn Thr Asn Ala Asn Arg Glu Glu 340 345 350			1477
ccc gtc agt ctc gcc ttc ccc aac ccc tac cag ttt gta tct tct gtt Pro Val Ser Leu Ala Phe Pro Asn Pro Tyr Gln Phe Val Ser Ser Val 355 360 365			1525
gac tac aat ccc cgg gac aac cag ctg tat gtg tgg aac aac tat ttc Asp Tyr Asn Pro Arg Asp Asn Gln Leu Tyr Val Trp Asn Asn Tyr Phe 370 375 380			1573
gtg gtg cgc tac agc ctg gag ttt gga ccc cca gat ccc agt gct ggc Val Val Arg Tyr Ser Leu Glu Phe Gly Pro Pro Asp Pro Ser Ala Gly 385 390 395			1621
cca gcc act tcc cca cct ctc agt acc acc acc aca gct cgg cct acg Pro Ala Thr Ser Pro Pro Leu Ser Thr Thr Thr Thr Ala Arg Pro Thr 400 405 410 415			1669
ccc ctc acc agc aca gcc tca cct gca gcc acc act cca ctc cgc cgg Pro Leu Thr Ser Thr Ala Ser Pro Ala Ala Thr Thr Pro Leu Arg Arg 420 425 430			1717
gcg ccc ctc acc acg cac cca gta ggt gcc atc aac cag ctg gga cct Ala Pro Leu Thr Thr His Pro Val Gly Ala Ile Asn Gln Leu Gly Pro 435 440 445			1765
gac ctg cct cca gcc aca gcc cca gca ccc agt acc cgg cgg cct cca Asp Leu Pro Pro Ala Thr Ala Pro Ala Pro Ser Thr Arg Arg Pro Pro 450 455 460			1813
gcc ccc aat ctg cat gtg tcc cct gag ctc ttc tgt gaa ccc cga gag Ala Pro Asn Leu His Val Ser Pro Glu Leu Phe Cys Glu Pro Arg Glu 465 470 475			1861
gtc cgg cgg gtc cag tgg cca gct acc cag cag ggt atg ctg gta gag Val Arg Arg Val Gln Trp Pro Ala Thr Gln Gln Gly Met Leu Val Glu 480 485 490 495			1909
aga cct tgc ccc aag gga act cga gga att gcc tgc ttc cag tgc ctc Arg Pro Cys Pro Lys Gly Thr Arg Gly Ile Ala Ser Phe Gln Cys Leu 500 505 510			1957
cca gct ctg ggg ctc tgg aat cct cgg ggc cct gac ctc agc aac tgc Pro Ala Leu Gly Leu Trp Asn Pro Arg Gly Pro Asp Leu Ser Asn Cys 515 520 525			2005
act tcc ccc tgg gtc aac caa gtc gcc cag aag atc aag agt gga gag Thr Ser Pro Trp Val Asn Gln Val Ala Gln Lys Ile Lys Ser Gly Glu 530 535 540			2053

aat gca gcc aac att gct agt gag ctg gcc cgc cac acg cgg ggc tcc Asn Ala Ala Asn Ile Ala Ser Glu Leu Ala Arg His Thr Arg Gly Ser 545 550 555	2101
atc tat gct ggg gac gtg tcc tca tcc gtg aag ctg atg gag caa ctg Ile Tyr Ala Gly Asp Val Ser Ser Ser Val Lys Leu Met Glu Gln Leu 560 565 570 575	2149
cta gat atc ctg gat gcc cag ctg cag gcc cta cgg ccc att gaa cga Leu Asp Ile Leu Asp Ala Gln Leu Gln Ala Leu Arg Pro Ile Glu Arg 580 585 590	2197
gag tca gct ggc aag aac tac aat aag atg cac aag cga gag aga acc Glu Ser Ala Gly Lys Asn Tyr Asn Lys Met His Lys Arg Glu Arg Thr 595 600 605	2245
tgc aag gac tat atc aag gct gtg gtg gag aca gtg gac aac ctg ctt Cys Lys Asp Tyr Ile Lys Ala Val Val Glu Thr Val Asp Asn Leu Leu 610 615 620	2293
cgg cca gag gca ctt gag tca tgg aaa gac atg aat gcc acc gaa cag Arg Pro Glu Ala Leu Glu Ser Trp Lys Asp Met Asn Ala Thr Glu Gln 625 630 635	2341
gtc cat acg gcc acc atg ctg cta gat gtc tta gag gag ggt gcc ttc Val His Thr Ala Thr Met Leu Leu Asp Val Leu Glu Glu Gly Ala Phe 640 645 650 655	2389
ctg ctg gcc gac aat gtc aga gaa cct gct cgc ttc ttg gct gcc aag Leu Leu Ala Asp Asn Val Arg Glu Pro Ala Arg Phe Leu Ala Ala Lys 660 665 670	2437
cag aat gtg gtc ctg gag gtc act gtc ctg agc aca gag ggt caa gtg Gln Asn Val Val Leu Glu Val Thr Val Leu Ser Thr Glu Gly Gln Val 675 680 685	2485
cag gag ttg gtg ttc ccc cag gag tat gcc agt gag agc tcc att cag Gln Glu Leu Val Phe Pro Gln Glu Tyr Ala Ser Glu Ser Ser Ile Gln 690 695 700	2533
ctg tcc gcc aac acc atc aag cag aac agc cgc aat ggt gtg gtg aag Leu Ser Ala Asn Thr Ile Lys Gln Asn Ser Arg Asn Gly Val Val Lys 705 710 715	2581
gtt gtc ttc att ctg tac aac aac ctg ggc ctg ttc ttg tcc acg gag Val Val Phe Ile Leu Tyr Asn Asn Leu Gly Leu Phe Leu Ser Thr Glu 720 725 730 735	2629
aat gcc aca gtg aag ctg gca ggt gag gca ggg acc ggt ggc cct gga Asn Ala Thr Val Lys Leu Ala Gly Glu Ala Gly Thr Gly Gly Pro Gly 740 745 750	2677
ggt gcc tcc ctg gtg gtt aac tca cag gtc atc gca gca tcc atc aat Gly Ala Ser Leu Val Val Asn Ser Gln Val Ile Ala Ala Ser Ile Asn 755 760 765	2725
aag gag tcc agc cgt gtc ttc ctg atg gac cct gtc atc ttt act gtg Lys Glu Ser Ser Arg Val Phe Leu Met Asp Pro Val Ile Phe Thr Val 770 775 780	2773
gcc cac ttg gag gcc aag aac cac ttc aat gca aac tgc tcc ttc tgg Ala His Leu Glu Ala Lys Asn His Phe Asn Ala Asn Cys Ser Phe Trp	2821

785	790	795	
aac tac tca gag cgc tcc atg ctg ggc tac tgg tca acc cag ggc tgc			2869
Asn Tyr Ser Glu Arg Ser Met Leu Gly Tyr Trp Ser Thr Gln Gly Cys			
800	805	810	815
cga ctg gtg gag tcc aat aag acc cat acc aca tgt gcc tgc agc cac			2917
Arg Leu Val Glu Ser Asn Lys Thr His Thr Thr Cys Ala Cys Ser His			
	820	825	830
ctc acc aac ttc gca gtg ctc atg gct cac cga gag atc tac caa ggc			2965
Leu Thr Asn Phe Ala Val Leu Met Ala His Arg Glu Ile Tyr Gln Gly			
	835	840	845
cgt att aat gag ctg ttg ctg tca gtc atc acc tgg gtt ggc att gtc			3013
Arg Ile Asn Glu Leu Leu Leu Ser Val Ile Thr Trp Val Gly Ile Val			
	850	855	860
atc tcc ctg gtc tgt ctg gct atc tgc atc tcc acc ttc tgc ttc ctg			3061
Ile Ser Leu Val Cys Leu Ala Ile Cys Ile Ser Thr Phe Cys Phe Leu			
	865	870	875
cgg ggc ctg cag acc gac cgc aac acc atc cac aag aac ctg tgc atc			3109
Arg Gly Leu Gln Thr Asp Arg Asn Thr Ile His Lys Asn Leu Cys Ile			
880	885	890	895
aac ctc ttc ctt gca gag ctg ctc ttc ctg gtt gga ata gac aaa act			3157
Asn Leu Phe Leu Ala Glu Leu Leu Phe Leu Val Gly Ile Asp Lys Thr			
	900	905	910
cag tat gag gtc gcc tgc cct atc ttt gcg ggc ctg ctg cac tac ttc			3205
Gln Tyr Glu Val Ala Cys Pro Ile Phe Ala Gly Leu Leu His Tyr Phe			
	915	920	925
ttc ctg gcc gcc ttc tcc tgg ctg tgc cta gag ggc gtg cac ctc tac			3253
Phe Leu Ala Ala Phe Ser Trp Leu Cys Leu Glu Gly Val His Leu Tyr			
	930	935	940
ctc ctg ctg gtc gag gtg ttc gag agc gaa tat tca cgc acc aag tac			3301
Leu Leu Leu Val Glu Val Phe Glu Ser Glu Tyr Ser Arg Thr Lys Tyr			
	945	950	955
tat tac ctg ggc ggc tac tgc ttc cca gcc ctg gtg gta ggc atc gca			3349
Tyr Tyr Leu Gly Gly Tyr Cys Phe Pro Ala Leu Val Val Gly Ile Ala			
960	965	970	975
gcc gcc att gac tac cga agc tac ggc act gag aag gcc tgc tgg ctg			3397
Ala Ala Ile Asp Tyr Arg Ser Tyr Gly Thr Glu Lys Ala Cys Trp Leu			
	980	985	990
agg gtg gat aac tat ttc atc tgg agc ttc att ggg ccc gtc tcc ttt			3445
Arg Val Asp Asn Tyr Phe Ile Trp Ser Phe Ile Gly Pro Val Ser Phe			
	995	1000	1005
gtt att gtg gtg aac ctg gtg ttc ctc atg gtg acc ctg cac aag atg			3493
Val Ile Val Val Asn Leu Val Phe Leu Met Val Thr Leu His Lys Met			
	1010	1015	1020
atc cga agc tca tcc gtg ctc aag cct gac tcc agc cgc ctt gac aac			3541
Ile Arg Ser Ser Ser Val Leu Lys Pro Asp Ser Ser Arg Leu Asp Asn			
1025	1030	1035	



atc aag tcc tgg gcg ctg ggt gcc att gca ctg ctc ttc ctg ctg ggc Ile Lys Ser Trp Ala Leu Gly Ala Ile Ala Leu Leu Phe Leu Leu Gly 1040 1045 1050 1055	3589
ctc acc tgg gct ttc ggc ctc ctc ttc atc aac aag gag tca gta gta Leu Thr Trp Ala Phe Gly Leu Leu Phe Ile Asn Lys Glu Ser Val Val 1060 1065 1070	3637
atg gct tac ctc ttc aca acc ttc aac gcc ttc cag ggg gtc ttc atc Met Ala Tyr Leu Phe Thr Thr Phe Asn Ala Phe Gln Gly Val Phe Ile 1075 1080 1085	3685
ttt gtc ttt cac tgc gcc tta cag aaa aag gtg cac aag gag tac agc Phe Val Phe His Cys Ala Leu Gln Lys Lys Val His Lys Glu Tyr Ser 1090 1095 1100	3733
aag tgc ctg cgt cac tcc tac tgc tgc att cgc tcc cca cct ggg ggg Lys Cys Leu Arg His Ser Tyr Cys Cys Ile Arg Ser Pro Pro Gly Gly 1105 1110 1115	3781
gct cac ggc tcc ctt aag acc tca gcc atg cga agt aac acc cgc tac Ala His Gly Ser Leu Lys Thr Ser Ala Met Arg Ser Asn Thr Arg Tyr 1120 1125 1130 1135	3829
tac aca ggg acc cag agc cga atc cgg agg atg tgg aat gac acc gtg Tyr Thr Gly Thr Gln Ser Arg Ile Arg Arg Met Trp Asn Asp Thr Val 1140 1145 1150	3877
agg aag cag aca gag tgc tcc ttt atg gca ggg gac atc aac agc acc Arg Lys Gln Thr Glu Ser Ser Phe Met Ala Gly Asp Ile Asn Ser Thr 1155 1160 1165	3925
ccc acc ctg aac cga ggt acc atg ggg aac cac cta ctg acc aac cct Pro Thr Leu Asn Arg Gly Thr Met Gly Asn His Leu Leu Thr Asn Pro 1170 1175 1180	3973
gtg cta cag ccc cgt ggg ggc act agc cca tac aat aca ctc att gca Val Leu Gln Pro Arg Gly Gly Thr Ser Pro Tyr Asn Thr Leu Ile Ala 1185 1190 1195	4021
gag tct gtg ggc ttc aat ccc tcc tgc ccc cca gtc ttc aac tcc cca Glu Ser Val Gly Phe Asn Pro Ser Ser Pro Pro Val Phe Asn Ser Pro 1200 1205 1210 1215	4069
gga agc tac agg gaa cct aag cac ccc ttg ggc ggc cgg gaa gcc tgt Gly Ser Tyr Arg Glu Pro Lys His Pro Leu Gly Gly Arg Glu Ala Cys 1220 1225 1230	4117
ggc atg gac aca ctg ccc ctt aat ggc aac ttc aac aac agc tac tcc Gly Met Asp Thr Leu Pro Leu Asn Gly Asn Phe Asn Asn Ser Tyr Ser 1235 1240 1245	4165
ttg cga agt ggt gat ttc cct ccg ggg gat ggg ggt cct gag cca ccc Leu Arg Ser Gly Asp Phe Pro Pro Gly Asp Gly Gly Pro Glu Pro Pro 1250 1255 1260	4213
cga ggc cga aac cta gcg gat gct gcg gcc ttt gag aag atg atc atc Arg Gly Arg Asn Leu Ala Asp Ala Ala Ala Phe Glu Lys Met Ile Ile 1265 1270 1275	4261
tca gag ctg gtg cac aac aac ctt cgg ggg gcc agt ggg ggc gcc aaa Ser Glu Leu Val His Asn Asn Leu Arg Gly Ala Ser Gly Gly Ala Lys	4309

1280	1285	1290	1295	
ggt cct cca cca gag cct cct gtg cca ccc gtg cca gga gtc agt gag				4357
Gly Pro Pro Pro Glu Pro Pro Val Pro Pro Val Pro Gly Val Ser Glu				
	1300	1305	1310	
gac gag gct ggt ggg cct ggg ggt gct gac cgg gct gag att gaa ctt				4405
Asp Glu Ala Gly Gly Pro Gly Gly Ala Asp Arg Ala Glu Ile Glu Leu				
	1315	1320	1325	
ctc tac aag gcc ctg gag gag cca ctg ctg ctg ccc cgg gcc cag tcc				4453
Leu Tyr Lys Ala Leu Glu Glu Pro Leu Leu Leu Pro Arg Ala Gln Ser				
	1330	1335	1340	
gtg ctg tac cag agt gat ctg gat gag tcc gag agc tgt acg gca gag				4501
Val Leu Tyr Gln Ser Asp Leu Asp Glu Ser Glu Ser Cys Thr Ala Glu				
	1345	1350	1355	
gat ggg gcc acc agc cgg ccc ctc tcc tcc cct ccc ggc cgg gac tcc				4549
Asp Gly Ala Thr Ser Arg Pro Leu Ser Ser Pro Pro Gly Arg Asp Ser				
	1360	1365	1370	1375
ctc tat gcc agc ggg gcc aac ctg cgg gac tcc ccc tcc tac ccg gac				4597
Leu Tyr Ala Ser Gly Ala Asn Leu Arg Asp Ser Pro Ser Tyr Pro Asp				
	1380	1385	1390	
agc agc ccc gaa ggg cct aat gag gcc ctg ccc cct ccc cca cct gct				4645
Ser Ser Pro Glu Gly Pro Asn Glu Ala Leu Pro Pro Pro Pro Ala				
	1395	1400	1405	
ccc cct ggg ccc cca gaa atc tac tac acc tct cgc cgg ccg gcc ctg				4693
Pro Pro Gly Pro Pro Glu Ile Tyr Tyr Thr Ser Arg Pro Pro Ala Leu				
	1410	1415	1420	
gtg gct cgg aat ccc cta cag ggc tac tac cag gtg cgg cgg ccc agc				4741
Val Ala Arg Asn Pro Leu Gln Gly Tyr Tyr Gln Val Arg Arg Pro Ser				
	1425	1430	1435	
cat gag ggc tac ctg gca gcc ccc agc ctt gag ggg cca ggg ccc gat				4789
His Glu Gly Tyr Leu Ala Ala Pro Ser Leu Glu Gly Pro Gly Pro Asp				
	1440	1445	1450	1455
ggg gat ggg caa atg cag ttg gtc act agt ctc tgaggggcct catggaccag				4842
Gly Asp Gly Gln Met Gln Leu Val Thr Ser Leu				
	1460	1465		
aggcctggcc agggagggaa tccaggaggg gctctggtgg gagcagagac tgatggaggc				4902
agtggctggt gggccactct ctccagggtgc ccctctgcct gtgggcccga cagtcacctt				4962
ggggactatg acctgggccc caggtgccag ggtagtaga cagggtttcc accagccaca				5022
agccccagct tctttagggg agtgcatgga ggagaagccc ccagggccct aggagtgagg				5082
gagaagctgg taggtgtgac caacgtccaa agctccctcc ctttggaggg agaaagcaag				5142
ggataaggct tccctagggtg tacaggggtg gccacttttg aggtggccga agccttgacg				5202
gatacacctc atctgctgct catcttcttc gtccaccaga aaggagcagt gggacagatg				5262
gacaggtcct tccatgctac agttccttgc ttcttggaga ctgggcctaa catcctgaga				5322

gaggccaggc ccaggggatg gatgggggtg tgaggggtgg tggtaaatgg tggaaacttc 5382  
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 gctatctggg gaggagatgt ggggtctggg gctccctgag gagtgggtcc tgggtttgga 5622  
 tctttcccta gggggtcttc ttacccttct cttctccccc tattgctgta aatatttcaa 5682  
 caaaatggaa a 5693

&lt;210&gt; 20

&lt;211&gt; 1466

&lt;212&gt; PRT

&lt;213&gt; Rattus rattus

&lt;400&gt; 20

Met Ala Arg Leu Ala Ala Ala Leu Trp Ser Leu Cys Val Thr Thr Val  
 1 5 10 15  
 Leu Val Thr Ser Ala Thr Gln Gly Leu Ser Arg Ala Gly Leu Pro Phe  
 20 25 30  
 Gly Leu Met Arg Arg Glu Leu Ala Cys Glu Gly Tyr Pro Ile Glu Leu  
 35 40 45  
 Arg Cys Pro Gly Ser Asp Val Ile Met Val Glu Asn Ala Asn Tyr Gly  
 50 55 60  
 Arg Thr Asp Asp Lys Ile Cys Asp Ala Asp Pro Phe Gln Met Glu Asn  
 65 70 75 80  
 Val Gln Cys Tyr Leu Pro Asp Ala Phe Lys Ile Met Ser Gln Arg Cys  
 85 90 95  
 Asn Asn Arg Thr Gln Cys Val Val Val Ala Gly Ser Asp Ala Phe Pro  
 100 105 110  
 Asp Pro Cys Pro Gly Thr Tyr Lys Tyr Leu Glu Val Gln Tyr Asp Cys  
 115 120 125  
 Val Pro Tyr Ile Phe Val Cys Pro Gly Thr Leu Gln Lys Val Leu Glu  
 130 135 140  
 Pro Thr Ser Thr His Glu Ser Glu His Gln Ser Gly Ala Trp Cys Lys  
 145 150 155 160  
 Asp Pro Leu Gln Ala Gly Asp Arg Ile Tyr Val Met Pro Trp Ile Pro  
 165 170 175  
 Tyr Arg Thr Asp Thr Leu Thr Glu Tyr Ala Ser Trp Glu Asp Tyr Val  
 180 185 190  
 Ala Ala Arg His Thr Thr Thr Tyr Arg Leu Pro Asn Arg Val Asp Gly  
 195 200 205  
 Thr Gly Phe Val Val Tyr Asp Gly Ala Val Phe Tyr Asn Lys Glu Arg  
 210 215 220

Thr Arg Asn Ile Val Lys Tyr Asp Leu Arg Thr Arg Ile Lys Ser Gly  
 225 230 235 240  
 Glu Thr Val Ile Asn Thr Ala Asn Tyr His Asp Thr Ser Pro Tyr Arg  
 245 250 255  
 Trp Gly Gly Lys Thr Asp Ile Asp Leu Ala Val Asp Glu Asn Gly Leu  
 260 265 270  
 Trp Val Ile Tyr Ala Thr Glu Gly Asn Asn Gly Arg Leu Val Val Ser  
 275 280 285  
 Gln Leu Asn Pro Tyr Thr Leu Arg Phe Glu Gly Thr Trp Glu Thr Gly  
 290 295 300  
 Tyr Asp Lys Arg Ser Ala Ser Asn Ala Phe Met Val Cys Gly Val Leu  
 305 310 315 320  
 Tyr Val Leu Arg Ser Val Tyr Val Asp Asp Asp Ser Glu Ala Ala Gly  
 325 330 335  
 Asn Arg Val Asp Tyr Ala Phe Asn Thr Asn Ala Asn Arg Glu Glu Pro  
 340 345 350  
 Val Ser Leu Ala Phe Pro Asn Pro Tyr Gln Phe Val Ser Ser Val Asp  
 355 360 365  
 Tyr Asn Pro Arg Asp Asn Gln Leu Tyr Val Trp Asn Asn Tyr Phe Val  
 370 375 380  
 Val Arg Tyr Ser Leu Glu Phe Gly Pro Pro Asp Pro Ser Ala Gly Pro  
 385 390 395 400  
 Ala Thr Ser Pro Pro Leu Ser Thr Thr Thr Thr Ala Arg Pro Thr Pro  
 405 410 415  
 Leu Thr Ser Thr Ala Ser Pro Ala Ala Thr Thr Pro Leu Arg Arg Ala  
 420 425 430  
 Pro Leu Thr Thr His Pro Val Gly Ala Ile Asn Gln Leu Gly Pro Asp  
 435 440 445  
 Leu Pro Pro Ala Thr Ala Pro Ala Pro Ser Thr Arg Arg Pro Pro Ala  
 450 455 460  
 Pro Asn Leu His Val Ser Pro Glu Leu Phe Cys Glu Pro Arg Glu Val  
 465 470 475 480  
 Arg Arg Val Gln Trp Pro Ala Thr Gln Gln Gly Met Leu Val Glu Arg  
 485 490 495  
 Pro Cys Pro Lys Gly Thr Arg Gly Ile Ala Ser Phe Gln Cys Leu Pro  
 500 505 510  
 Ala Leu Gly Leu Trp Asn Pro Arg Gly Pro Asp Leu Ser Asn Cys Thr  
 515 520 525  
 Ser Pro Trp Val Asn Gln Val Ala Gln Lys Ile Lys Ser Gly Glu Asn  
 530 535 540  
 Ala Ala Asn Ile Ala Ser Glu Leu Ala Arg His Thr Arg Gly Ser Ile  
 545 550 555 560

Tyr Ala Gly Asp Val Ser Ser Ser Val Lys Leu Met Glu Gln Leu Leu  
 565 570 575  
 Asp Ile Leu Asp Ala Gln Leu Gln Ala Leu Arg Pro Ile Glu Arg Glu  
 580 585 590  
 Ser Ala Gly Lys Asn Tyr Asn Lys Met His Lys Arg Glu Arg Thr Cys  
 595 600 605  
 Lys Asp Tyr Ile Lys Ala Val Val Glu Thr Val Asp Asn Leu Leu Arg  
 610 615 620  
 Pro Glu Ala Leu Glu Ser Trp Lys Asp Met Asn Ala Thr Glu Gln Val  
 625 630 635 640  
 His Thr Ala Thr Met Leu Leu Asp Val Leu Glu Glu Gly Ala Phe Leu  
 645 650 655  
 Leu Ala Asp Asn Val Arg Glu Pro Ala Arg Phe Leu Ala Ala Lys Gln  
 660 665 670  
 Asn Val Val Leu Glu Val Thr Val Leu Ser Thr Glu Gly Gln Val Gln  
 675 680 685  
 Glu Leu Val Phe Pro Gln Glu Tyr Ala Ser Glu Ser Ser Ile Gln Leu  
 690 695 700  
 Ser Ala Asn Thr Ile Lys Gln Asn Ser Arg Asn Gly Val Val Lys Val  
 705 710 715 720  
 Val Phe Ile Leu Tyr Asn Asn Leu Gly Leu Phe Leu Ser Thr Glu Asn  
 725 730 735  
 Ala Thr Val Lys Leu Ala Gly Glu Ala Gly Thr Gly Gly Pro Gly Gly  
 740 745 750  
 Ala Ser Leu Val Val Asn Ser Gln Val Ile Ala Ala Ser Ile Asn Lys  
 755 760 765  
 Glu Ser Ser Arg Val Phe Leu Met Asp Pro Val Ile Phe Thr Val Ala  
 770 775 780  
 His Leu Glu Ala Lys Asn His Phe Asn Ala Asn Cys Ser Phe Trp Asn  
 785 790 795 800  
 Tyr Ser Glu Arg Ser Met Leu Gly Tyr Trp Ser Thr Gln Gly Cys Arg  
 805 810 815  
 Leu Val Glu Ser Asn Lys Thr His Thr Thr Cys Ala Cys Ser His Leu  
 820 825 830  
 Thr Asn Phe Ala Val Leu Met Ala His Arg Glu Ile Tyr Gln Gly Arg  
 835 840 845  
 Ile Asn Glu Leu Leu Leu Ser Val Ile Thr Trp Val Gly Ile Val Ile  
 850 855 860  
 Ser Leu Val Cys Leu Ala Ile Cys Ile Ser Thr Phe Cys Phe Leu Arg  
 865 870 875 880  
 Gly Leu Gln Thr Asp Arg Asn Thr Ile His Lys Asn Leu Cys Ile Asn  
 885 890 895

Leu Phe Leu Ala Glu Leu Leu Phe Leu Val Gly Ile Asp Lys Thr Gln  
 900 905 910  
 Tyr Glu Val Ala Cys Pro Ile Phe Ala Gly Leu Leu His Tyr Phe Phe  
 915 920 925  
 Leu Ala Ala Phe Ser Trp Leu Cys Leu Glu Gly Val His Leu Tyr Leu  
 930 935 940  
 Leu Leu Val Glu Val Phe Glu Ser Glu Tyr Ser Arg Thr Lys Tyr Tyr  
 945 950 955 960  
 Tyr Leu Gly Gly Tyr Cys Phe Pro Ala Leu Val Val Gly Ile Ala Ala  
 965 970 975  
 Ala Ile Asp Tyr Arg Ser Tyr Gly Thr Glu Lys Ala Cys Trp Leu Arg  
 980 985 990  
 Val Asp Asn Tyr Phe Ile Trp Ser Phe Ile Gly Pro Val Ser Phe Val  
 995 1000 1005  
 Ile Val Val Asn Leu Val Phe Leu Met Val Thr Leu His Lys Met Ile  
 1010 1015 1020  
 Arg Ser Ser Ser Val Leu Lys Pro Asp Ser Ser Arg Leu Asp Asn Ile  
 1025 1030 1035 104  
 Lys Ser Trp Ala Leu Gly Ala Ile Ala Leu Leu Phe Leu Leu Gly Leu  
 1045 1050 1055  
 Thr Trp Ala Phe Gly Leu Leu Phe Ile Asn Lys Glu Ser Val Val Met  
 1060 1065 1070  
 Ala Tyr Leu Phe Thr Thr Phe Asn Ala Phe Gln Gly Val Phe Ile Phe  
 1075 1080 1085  
 Val Phe His Cys Ala Leu Gln Lys Lys Val His Lys Glu Tyr Ser Lys  
 1090 1095 1100  
 Cys Leu Arg His Ser Tyr Cys Cys Ile Arg Ser Pro Pro Gly Gly Ala  
 1105 1110 1115 112  
 His Gly Ser Leu Lys Thr Ser Ala Met Arg Ser Asn Thr Arg Tyr Tyr  
 1125 1130 1135  
 Thr Gly Thr Gln Ser Arg Ile Arg Arg Met Trp Asn Asp Thr Val Arg  
 1140 1145 1150  
 Lys Gln Thr Glu Ser Ser Phe Met Ala Gly Asp Ile Asn Ser Thr Pro  
 1155 1160 1165  
 Thr Leu Asn Arg Gly Thr Met Gly Asn His Leu Leu Thr Asn Pro Val  
 1170 1175 1180  
 Leu Gln Pro Arg Gly Gly Thr Ser Pro Tyr Asn Thr Leu Ile Ala Glu  
 1185 1190 1195 120  
 Ser Val Gly Phe Asn Pro Ser Ser Pro Pro Val Phe Asn Ser Pro Gly  
 1205 1210 1215  
 Ser Tyr Arg Glu Pro Lys His Pro Leu Gly Gly Arg Glu Ala Cys Gly  
 1220 1225 1230

Met Asp Thr Leu Pro Leu Asn Gly Asn Phe Asn Asn Ser Tyr Ser Leu  
 1235 1240 1245

Arg Ser Gly Asp Phe Pro Pro Gly Asp Gly Gly Pro Glu Pro Pro Arg  
 1250 1255 1260

Gly Arg Asn Leu Ala Asp Ala Ala Ala Phe Glu Lys Met Ile Ile Ser  
 265 1270 1275 128

Glu Leu Val His Asn Asn Leu Arg Gly Ala Ser Gly Gly Ala Lys Gly  
 1285 1290 1295

Pro Pro Pro Glu Pro Pro Val Pro Pro Val Pro Gly Val Ser Glu Asp  
 1300 1305 1310

Glu Ala Gly Gly Pro Gly Gly Ala Asp Arg Ala Glu Ile Glu Leu Leu  
 1315 1320 1325

Tyr Lys Ala Leu Glu Glu Pro Leu Leu Leu Pro Arg Ala Gln Ser Val  
 1330 1335 1340

Leu Tyr Gln Ser Asp Leu Asp Glu Ser Glu Ser Cys Thr Ala Glu Asp  
 345 1350 1355 136

Gly Ala Thr Ser Arg Pro Leu Ser Ser Pro Pro Gly Arg Asp Ser Leu  
 1365 1370 1375

Tyr Ala Ser Gly Ala Asn Leu Arg Asp Ser Pro Ser Tyr Pro Asp Ser  
 1380 1385 1390

Ser Pro Glu Gly Pro Asn Glu Ala Leu Pro Pro Pro Pro Ala Pro  
 1395 1400 1405

Pro Gly Pro Pro Glu Ile Tyr Tyr Thr Ser Arg Pro Pro Ala Leu Val  
 1410 1415 1420

Ala Arg Asn Pro Leu Gln Gly Tyr Tyr Gln Val Arg Arg Pro Ser His  
 425 1430 1435 144

Glu Gly Tyr Leu Ala Ala Pro Ser Leu Glu Gly Pro Gly Pro Asp Gly  
 1445 1450 1455

Asp Gly Gln Met Gln Leu Val Thr Ser Leu  
 1460 1465

&lt;210&gt; 21

&lt;211&gt; 829

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 21

agtgggttggg gtttcagctg ctattgacta taagagctat ggaacagaaa aagcttgctg 60

gcttcattgtt gataactact ttatatggag cttcattgga cctgttacct tcattattct 120

gctaaatatt atcttcttgg tgatcacatt gtgcaaaatg gtgaagcatt caaacacttt 180

gaaaccagat tctagcaggt tggaaaacat taagtcttgg gtgcttggcg ctttcgctct 240

tctgtgtctt cttggcctca cctggctcct tgggttgctt tttattaatg aggagactat 300

tgtgatggca tatctcttca ctatatttaa tgccttccag ggagtgttca ttttcatctt 360  
 tcaactgtgt ctccaaaaga aagtaagaaa agaatatggc aagtgttca gacactcata 420  
 ctgctgtgga ggctcccaa ctgagagtc ccacagttca gtgaaggcat caaccaccag 480  
 aaccagtgtt cgctattcct ctggcacaca gagtctgata agaagaatgt ggaatgatac 540  
 tgtgagaaaa caatcagaat cttcttttat ctgaggtgac atcaatagca cttcaacact 600  
 taatcaagga cattcactga acaatgccag ggatacaagt gccatggata ctctaccgct 660  
 aaatggtaat tttaacaaca gctactcgtt gcacaagggt gactataatg acagcgtgca 720  
 agttgtggac tgtggactaa gtctgaatga tactgctttt gagaaaatga tcatttcaga 780  
 attagtgcac aacaacttac ggggcagcag caagactcac aacctcgag 829

<210> 22  
 <211> 429  
 <212> DNA  
 <213> Homo sapiens

<400> 22  
 ggggactggt gccccacgc gtgtcagcac ggggttggtc agcaggtggt tccccatggt 60  
 acctcggttc aggggtgggg tgcgttgat gtcacccgc atgaaggagg actccgtctg 120  
 tttccacaca gtgtcattcc acatccctcg aattcggtc tgggtccctg tgtagtagcg 180  
 ggtgttgctt cgcattggtg aggtcttgag ggatccgtga gtgccccgg gtgggatgcg 240  
 gatgcagcag taggagtgac gcaggcactt gctgtactcc ttgtgcacct tcttctgtaa 300  
 ggcgagtgta aagacgaaga tgaagacccc ctggaaggcg ttgaagggtg tgaagagata 360  
 ggccatgacc accgactcct tgttgatgaa gaggaggccg aaagcccagg tgaggcccag 420  
 caggaacag 429

<210> 23  
 <211> 280  
 <212> DNA  
 <213> Homo sapiens

<400> 23  
 ctgagtcttg tcgatccga ccaggaagag cagctcagcc aggaagaggt tgatgcacag 60  
 gttcttgttg atggtgttgc ggtcggctct cagccccgc agaagcagaa ggtggagatg 120  
 cagatggcca agcagaccag ggagatcaca atgcccaccc aggtgatgac cgacagcagc 180  
 agctcgttga tgcggccctg gtagatctca cggtagacca tgagcacagc gaagttggtg 240  
 aggtggctgc aggcacacgt ggtatgggtc ttgttgact 280

<210> 24  
 <211> 24  
 <212> DNA



<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 24

tcttcagctg agctcttcaa aacc

24

<210> 25

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 25

ggttttgaag agctcagctg aaga

24

<210> 26

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 26

cagcagggat ccaccatggt gtcttctggt tgcagaatgc gaagtctgtg g

51

<210> 27

<211> 55

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 27

gacgatgacg cggccgccta ttaaagactt gtaaccagct gcatttgtcc ttctc

55

<210> 28

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 28

tacaaccatg ggcacaactg tagctgg

27

<210> 29

<211> 34

<212> DNA

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 29

tacaagatct agcagatagc caggcaaaca aggg

34

&lt;210&gt; 30

&lt;211&gt; 439

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

aaaagcagta tcattcagac ttagtcacaa gtccacaact tgcacgctgt cattatagtc 60  
 acccttggtgc agcgagtagt gtntgttaaa attaccattt agcggtagag tatccatggc 120  
 acttgatatcc ctgggcattg ttcagtgaat gtccttgatt aagtgttgaa gtgctattga 180  
 tgtcacctga gataaaagaa gattctgatt gttttctcac agtatcattc cacattcttc 240  
 ttatacggac tctgtgtgcc agagggaata gcgagcactg ggttctgggt gggttgatgc 300  
 cttcactgaa ctgtgggggg actctcaggt tggggagggc ctncacaggc agtatggagg 360  
 tgtcttgaag gcactttgcc ataattcttt ttctgtacctt tccttttggg agagcacagt 420  
 gaaagntgga aaattgacc

439

&lt;210&gt; 31

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 31

tacaaccatg ggcacaactg tagctgg

27

&lt;210&gt; 32

&lt;211&gt; 34

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 32

tacaagatct agcagatagc caggcaaaca aggg

34

&lt;210&gt; 33

&lt;211&gt; 5598

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (407)..(3748)

66

Ala Ile Ile Asn Tyr	Ala Asn Tyr His Asp Thr Ser Pro Tyr Arg Trp	
180	185	190 195
gga gga aag act gat atc gac cta gca gtt gat gaa aat ggt tta tgg		1039
Gly Gly Lys Thr	Asp Ile Asp Leu Ala Val Asp Glu Asn Gly Leu Trp	
	200 205 210	
gtc att tac gcc act gaa cag aac aat gga atg ata gtt att agc cag		1087
Val Ile Tyr	Ala Thr Glu Gln Asn Asn Gly Met Ile Val Ile Ser Gln	
	215 220 225	
ctg aat cca tac act ctt cga ttt gaa gca acg tgg gag act gta tac		1135
Leu Asn Pro Tyr Thr Leu Arg Phe Glu Ala Thr Trp Glu Thr Val Tyr		
	230 235 240	
gac aaa cgt gcc gca tca aat gct ttt atg ata tgc gga gtc ctc tat		1183
Asp Lys Arg Ala Ala Ser Asn Ala Phe Met Ile Cys Gly Val Leu Tyr		
	245 250 255	
gtg gtt agg tca gtt tat caa gac aat gaa agt gaa aca ggc aag aac		1231
Val Val Arg Ser Val Tyr Gln Asp Asn Glu Ser Glu Thr Gly Lys Asn		
	260 265 270 275	
tca att gat tac att tat aat acc cga tta aac cga gga gaa tat gta		1279
Ser Ile Asp Tyr Ile Tyr Asn Thr Arg Leu Asn Arg Gly Glu Tyr Val		
	280 285 290	
gac gtt ccc ttc ccc aac cag tat cag tat att gct gca gtg gat tac		1327
Asp Val Pro Phe Pro Asn Gln Tyr Gln Tyr Ile Ala Ala Val Asp Tyr		
	295 300 305	
aat cca aga gat aac caa ctt tac gtg tgg aac aat aac ttc att tta		1375
Asn Pro Arg Asp Asn Gln Leu Tyr Val Trp Asn Asn Asn Phe Ile Leu		
	310 315 320	
cga tat tct ctg gag ttt ggt cca cct gat cct gcc caa gtg cct acc		1423
Arg Tyr Ser Leu Glu Phe Gly Pro Pro Asp Pro Ala Gln Val Pro Thr		
	325 330 335	
aca gct gtg aca ata act tct tca gct gag ctg ttc aaa acc ata ata		1471
Thr Ala Val Thr Ile Thr Ser Ala Glu Leu Phe Lys Thr Ile Ile		
	340 345 350 355	
tca acc aca agc act act tca cag aaa ggc ccc atg agc aca act gta		1519
Ser Thr Thr Ser Thr Thr Ser Gln Lys Gly Pro Met Ser Thr Thr Val		
	360 365 370	
gct gga tca cag gaa gga agc aaa ggg aca aaa cca cct cca gca gtt		1567
Ala Gly Ser Gln Glu Gly Ser Lys Gly Thr Lys Pro Pro Pro Ala Val		
	375 380 385	
tct aca acc aaa att cca cct ata aca aat att ttt ccc ctg cca gag		1615
Ser Thr Thr Lys Ile Pro Pro Ile Thr Asn Ile Phe Pro Leu Pro Glu		
	390 395 400	
aga ttc tgt gaa gca tta gac tcc aag ggg ata aag tgg cct cag aca		1663
Arg Phe Cys Glu Ala Leu Asp Ser Lys Gly Ile Lys Trp Pro Gln Thr		
	405 410 415	
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Gln Arg Gly Met Met Val Glu Arg Pro Cys Pro Lys Gly Thr Arg Gly		
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Thr Ala Ser Tyr Leu Cys Met Ile Ser Thr Gly Thr Trp Asn Pro Lys	
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ggc gcc gat ctt agc aac tgt acc tca cac tgg gtg aat cag ctg gct	1807
Gly Pro Asp Leu Ser Asn Cys Thr Ser His Trp Val Asn Gln Leu Ala	
455 460 465	
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Gln Lys Ile Arg Ser Gly Glu Asn Ala Ala Ser Leu Ala Asn Glu Leu	
470 475 480	
gct aaa cat acc aaa ggg cca gtg ttt gct ggg gat gta agt tct tca	1903
Ala Lys His Thr Lys Gly Pro Val Phe Ala Gly Asp Val Ser Ser Ser	
485 490 495	
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Val Arg Leu Met Glu Gln Leu Val Asp Ile Leu Asp Ala Gln Leu Gln	
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Glu Leu Lys Pro Ser Glu Lys Asp Ser Ala Gly Arg Ser Tyr Asn Lys	
520 525 530	
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Ala Ile Val Asp Thr Val Asp Asn Leu Leu Arg Pro Glu Ala Leu Glu	
535 540 545	
tca tgg aaa cat atg aat tct tct gaa caa gca cat act gca aca atg	2095
Ser Trp Lys His Met Asn Ser Ser Glu Gln Ala His Thr Ala Thr Met	
550 555 560	
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Leu Leu Asp Thr Leu Glu Glu Gly Ala Phe Val Leu Ala Asp Asn Leu	
565 570 575	
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Leu Glu Pro Thr Arg Val Ser Met Pro Thr Glu Asn Ile Val Leu Glu	
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Val Ala Val Leu Ser Thr Glu Gly Gln Ile Gln Asp Phe Lys Phe Pro	
600 605 610	
ctg ggc atc aaa gga gca ggc agc tca atc caa ctg tcc gca aat acc	2287
Leu Gly Ile Lys Gly Ala Gly Ser Ser Ile Gln Leu Ser Ala Asn Thr	
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gtc aaa cag aac agc agg aat ggg ctt gca aag ttg gtg ttc atc att	2335
Val Lys Gln Asn Ser Arg Asn Gly Leu Ala Lys Leu Val Phe Ile Ile	
630 635 640	
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Tyr Arg Ser Leu Gly Gln Phe Leu Ser Thr Glu Asn Ala Thr Ile Lys	
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ctg ggt gct gat ttt att ggt cgt aat agc acc att gca gtg aac tct	2431
Leu Gly Ala Asp Phe Ile Gly Arg Asn Ser Thr Ile Ala Val Asn Ser	
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cac gtc att tca gtt tca atc aat aaa gag tcc agc cga gta tac ctg	2479
His Val Ile Ser Val Ser Ile Asn Lys Glu Ser Ser Arg Val Tyr Leu	

680										685										690									
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Thr	Asp	Pro	Val	Leu	Phe	Thr	Leu	Pro	His	Ile	Asp	Pro	Asp	Asn	Tyr														
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Phe	Asn	Ala	Asn	Cys	Ser	Phe	Trp	Asn	Tyr	Ser	Glu	Arg	Thr	Met	Met														
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Gly	Tyr	Trp	Ser	Thr	Gln	Gly	Cys	Lys	Leu	Val	Asp	Thr	Asn	Lys	Thr														
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gcc	cac	agg	gaa	att	gca	tat	aaa	gat	ggc	ggt	cat	gaa	tta	ctt	ctt														
Ala	His	Arg	Glu	Ile	Ala	Tyr	Lys	Asp	Gly	Val	His	Glu	Leu	Leu	Leu														
aca	gtc	atc	acc	tgg	gtg	gga	att	gtc	att	tcc	ctt	ggt	tgc	ctg	gct														
Thr	Val	Ile	Thr	Trp	Val	Gly	Ile	Val	Ile	Ser	Leu	Val	Cys	Leu	Ala														
atc	tgc	atc	ttc	acc	ttc	tgc	ttt	ttc	cgt	ggc	cta	cag	agt	gac	cga														
Ile	Cys	Ile	Phe	Thr	Phe	Cys	Phe	Phe	Arg	Gly	Leu	Gln	Ser	Asp	Arg														
aat	act	att	cac	aag	aac	ctt	tgt	atc	aac	ctt	ttc	att	gct	gaa	ttt														
Asn	Thr	Ile	His	Lys	Asn	Leu	Cys	Ile	Asn	Leu	Phe	Ile	Ala	Glu	Phe														
att	ttc	cta	ata	ggc	att	gat	aag	aca	aaa	tat	gcg	att	gca	tgc	cca														
Ile	Phe	Leu	Ile	Gly	Ile	Asp	Lys	Thr	Lys	Tyr	Ala	Ile	Ala	Cys	Pro														
ata	ttt	gca	gga	ctt	cta	cac	ttt	ttc	ttt	ttg	gca	gct	ttt	gct	tgg														
Ile	Phe	Ala	Gly	Leu	Leu	His	Phe	Phe	Phe	Leu	Ala	Ala	Phe	Ala	Trp														
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Met	Cys	Leu	Glu	Gly	Val	Gln	Leu	Tyr	Leu	Met	Leu	Val	Glu	Val	Phe														
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Glu	Ser	Glu	Tyr	Ser	Arg	Lys	Lys	Tyr	Tyr	Tyr	Val	Ala	Gly	Tyr	Leu														
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Phe	Pro	Ala	Thr	Val	Val	Gly	Val	Ser	Ala	Ala	Ile	Asp	Tyr	Lys	Ser														
tat	gga	aca	gaa	aaa	gct	tgc	tgg	ctt	cat	ggt	gat	aac	tac	ttt	ata														
Tyr	Gly	Thr	Glu	Lys	Ala	Cys	Trp	Leu	His	Val	Asp	Asn	Tyr	Phe	Ile														
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Trp	Ser	Phe	Ile	Gly	Pro	Val	Thr	Phe	Ile	Ile	Leu	Leu	Asn	Ile	Ile														

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 Phe Leu Val Ile Thr Leu Cys Lys Met Val Lys His Ser Asn Thr Leu  
 935 940 945

aaa cca gat tct agc agg ttg gaa aac att aag tct tgg gtg ctt ggc 3295  
 Lys Pro Asp Ser Ser Arg Leu Glu Asn Ile Lys Ser Trp Val Leu Gly  
 950 955 960

gct ttc gct ctt ctg tgt ctt ctt ggc ctc acc tgg tcc ttt ggg ttg 3343  
 Ala Phe Ala Leu Leu Cys Leu Leu Gly Leu Thr Trp Ser Phe Gly Leu  
 965 970 975

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tgc tgt gga ggc ctc cca act gag agt ccc cac agt tca gtg aag gca 3535  
 Cys Cys Gly Gly Leu Pro Thr Glu Ser Pro His Ser Ser Val Lys Ala  
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 1060 1065 1070 1075

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 1080 1085 1090

aca tca cat ggt ctg aga gcc cat ctt caa gat tta tat cat tta gag 3727  
 Thr Ser His Gly Leu Arg Ala His Leu Gln Asp Leu Tyr His Leu Glu  
 1095 1100 1105

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&lt;210&gt; 34

&lt;211&gt; 1114

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 34

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Glu	Asn	Thr	Asp	Cys	Tyr	Leu	Pro	Asp	Ala	Phe	Lys	Ile	Met	Thr	Gln
	20							25					30		

Arg	Cys	Asn	Asn	Arg	Thr	Gln	Cys	Ile	Val	Val	Thr	Gly	Ser	Asp	Val
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Phe Pro Asp Pro Cys Pro Gly Thr Tyr Lys Tyr Leu Glu Val Gln Tyr			
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Glu Cys Val Pro Tyr Ile Phe Val Cys Pro Gly Thr Leu Lys Ala Ile			
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Val Asp Ser Pro Cys Ile Tyr Glu Ala Glu Gln Lys Ala Gly Ala Trp			
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Cys Lys Asp Pro Leu Gln Ala Ala Asp Lys Ile Tyr Phe Met Pro Trp			
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Thr Pro Tyr Arg Thr Asp Thr Leu Ile Glu Tyr Ala Ser Leu Glu Asp			
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Phe Gln Asn Ser Arg Gln Thr Thr Thr Tyr Lys Leu Pro Asn Arg Val			
130	135	140	
Asp Gly Thr Gly Phe Val Val Tyr Asp Gly Ala Val Phe Phe Asn Lys			
145	150	155	160
Glu Arg Thr Arg Asn Ile Val Lys Phe Asp Leu Arg Thr Arg Ile Lys			
165	170	175	
Ser Gly Glu Ala Ile Ile Asn Tyr Ala Asn Tyr His Asp Thr Ser Pro			
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Tyr Arg Trp Gly Gly Lys Thr Asp Ile Asp Leu Ala Val Asp Glu Asn			
195	200	205	
Gly Leu Trp Val Ile Tyr Ala Thr Glu Gln Asn Asn Gly Met Ile Val			
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Ile Ser Gln Leu Asn Pro Tyr Thr Leu Arg Phe Glu Ala Thr Trp Glu			
225	230	235	240
Thr Val Tyr Asp Lys Arg Ala Ala Ser Asn Ala Phe Met Ile Cys Gly			
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Val Leu Tyr Val Val Arg Ser Val Tyr Gln Asp Asn Glu Ser Glu Thr			
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Gly Lys Asn Ser Ile Asp Tyr Ile Tyr Asn Thr Arg Leu Asn Arg Gly			
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Glu Tyr Val Asp Val Pro Phe Pro Asn Gln Tyr Gln Tyr Ile Ala Ala			
290	295	300	
Val Asp Tyr Asn Pro Arg Asp Asn Gln Leu Tyr Val Trp Asn Asn Asn			
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Phe Ile Leu Arg Tyr Ser Leu Glu Phe Gly Pro Pro Asp Pro Ala Gln			
325	330	335	
Val Pro Thr Thr Ala Val Thr Ile Thr Ser Ser Ala Glu Leu Phe Lys			
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Thr Ile Ile Ser Thr Thr Ser Thr Thr Ser Gln Lys Gly Pro Met Ser			
355	360	365	

Thr Thr Val Ala Gly Ser Gln Glu Gly Ser Lys Gly Thr Lys Pro Pro  
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 Pro Ala Val Ser Thr Thr Lys Ile Pro Pro Ile Thr Asn Ile Phe Pro  
 385 390 395 400  
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 405 410 415  
 Pro Gln Thr Gln Arg Gly Met Met Val Glu Arg Pro Cys Pro Lys Gly  
 420 425 430  
 Thr Arg Gly Thr Ala Ser Tyr Leu Cys Met Ile Ser Thr Gly Thr Trp  
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 545 550 555 560  
 Ala Thr Met Leu Leu Asp Thr Leu Glu Glu Gly Ala Phe Val Leu Ala  
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 Asp Asn Leu Leu Glu Pro Thr Arg Val Ser Met Pro Thr Glu Asn Ile  
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 Val Leu Glu Val Ala Val Leu Ser Thr Glu Gly Gln Ile Gln Asp Phe  
 595 600 605  
 Lys Phe Pro Leu Gly Ile Lys Gly Ala Gly Ser Ser Ile Gln Leu Ser  
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 Ala Asn Thr Val Lys Gln Asn Ser Arg Asn Gly Leu Ala Lys Leu Val  
 625 630 635 640  
 Phe Ile Ile Tyr Arg Ser Leu Gly Gln Phe Leu Ser Thr Glu Asn Ala  
 645 650 655  
 Thr Ile Lys Leu Gly Ala Asp Phe Ile Gly Arg Asn Ser Thr Ile Ala  
 660 665 670  
 Val Asn Ser His Val Ile Ser Val Ser Ile Asn Lys Glu Ser Ser Arg  
 675 680 685  
 Val Tyr Leu Thr Asp Pro Val Leu Phe Thr Leu Pro His Ile Asp Pro  
 690 695 700

Asp Asn Tyr Phe Asn Ala Asn Cys Ser Phe Trp Asn Tyr Ser Glu Arg  
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 Thr Met Met Gly Tyr Trp Ser Thr Gln Gly Cys Lys Leu Val Asp Thr  
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 740 745 750  
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 755 760 765  
 Leu Leu Leu Thr Val Ile Thr Trp Val Gly Ile Val Ile Ser Leu Val  
 770 775 780  
 Cys Leu Ala Ile Cys Ile Phe Thr Phe Cys Phe Phe Arg Gly Leu Gln  
 785 790 795 800  
 Ser Asp Arg Asn Thr Ile His Lys Asn Leu Cys Ile Asn Leu Phe Ile  
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 850 855 860  
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 865 870 875 880  
 Gly Tyr Leu Phe Pro Ala Thr Val Val Gly Val Ser Ala Ala Ile Asp  
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 900 905 910  
 Tyr Phe Ile Trp Ser Phe Ile Gly Pro Val Thr Phe Ile Ile Leu Leu  
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 Asn Ile Ile Phe Leu Val Ile Thr Leu Cys Lys Met Val Lys His Ser  
 930 935 940  
 Asn Thr Leu Lys Pro Asp Ser Ser Arg Leu Glu Asn Ile Lys Ser Trp  
 945 950 955 960  
 Val Leu Gly Ala Phe Ala Leu Leu Cys Leu Leu Gly Leu Thr Trp Ser  
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22

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 <212> DNA  
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 <212> DNA  
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 <212> DNA  
 <213> Homo sapiens

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<212> DNA  
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&lt;211&gt; 21

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 49

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21

&lt;210&gt; 50

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 50

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19

&lt;210&gt; 51

&lt;211&gt; 40

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

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40

&lt;210&gt; 52

&lt;211&gt; 37

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 52

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 <213> Homo sapiens

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<210> 57  
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Met Ala Arg Leu Ala  
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Ala Val Leu Trp Asn Leu Cys Val Thr Ala Val Leu Val Thr Ser Ala  
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Thr Gln Gly Leu Ser Arg Ala Gly Leu Pro Phe Gly Leu Met Arg Arg  
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ccg gac gcc ttc aag atc atg tca cag agg tgt aac aac cgc acc cag 583  
Pro Asp Ala Phe Lys Ile Met Ser Gln Arg Cys Asn Asn Arg Thr Gln  
90 95 100

tgc gtg gtg gtc gcc ggc tcg gat gcc ttt cct gac ccc tgt cct ggg 631  
Cys Val Val Val Ala Gly Ser Asp Ala Phe Pro Asp Pro Cys Pro Gly  
105 110 115

acc tac aag tac ctg gag gtg cag tac gac tgt gtc ccc tac atc ttc 679  
Thr Tyr Lys Tyr Leu Glu Val Gln Tyr Asp Cys Val Pro Tyr Ile Phe  
120 125 130

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Val Cys Pro Gly Thr Leu Gln Lys Val Leu Glu Pro Thr Ser Thr His  
135 140 145

gag tca gag cac cag tct ggc gca tgg tgc aag gac ccg ctg cag gcg 775  
Glu Ser Glu His Gln Ser Gly Ala Trp Cys Lys Asp Pro Leu Gln Ala  
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Gly Asp Arg Ile Tyr Val Met Pro Trp Ile Pro Tyr Arg Thr Asp Thr  
170 175 180

ctg act gag tat gcc tcg tgg gag gac tac gtg gcc gcc cgc cac acc 871  
Leu Thr Glu Tyr Ala Ser Trp Glu Asp Tyr Val Ala Ala Arg His Thr  
185 190 195

acc acc tac cgc ctg ccc aac cgc gtg gat gcc aca gcc ttt gtg gtc 919  
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200 205 210

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 Ala Ser Asn Ala Phe Met Val Cys Gly Val Leu Tyr Val Leu Arg Ser  
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 Ser Pro Ala Ala Thr Thr Pro Leu Arg Arg Ala Pro Leu Thr Thr His  
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			600				605					610																	
gcc	gtg	gtg	gag	aca	gtg	gac	aat	ctg	ctc	cgg	cca	gaa	gct	ctg	gag														
Ala	Val	Val	Glu	Thr	Val	Asp	Asn	Leu	Leu	Arg	Pro	Glu	Ala	Leu	Glu														
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Ser	Trp	Lys	Asp	Met	Asn	Ala	Thr	Glu	Gln	Val	His	Thr	Ala	Thr	Met														
			630				635				640				645														
ctc	ctc	gac	gtc	ctg	gag	gag	ggc	gcc	ttc	ctg	ctg	gcc	gac	aat	gtc														
Leu	Leu	Asp	Val	Leu	Glu	Glu	Gly	Ala	Phe	Leu	Leu	Ala	Asp	Asn	Val														
				650				655						660															
agg	gag	cct	gcc	cgc	ttc	ctg	gct	gcc	aag	gag	aac	gtg	gtc	ctg	gag														
Arg	Glu	Pro	Ala	Arg	Phe	Leu	Ala	Ala	Lys	Glu	Asn	Val	Val	Leu	Glu														
			665				670						675																
gtc	aca	gtc	ctg	aac	aca	gag	ggc	cag	gtg	cag	gag	ctg	gtg	ttc	ccc														
Val	Thr	Val	Leu	Asn	Thr	Glu	Gly	Gln	Val	Gln	Glu	Leu	Val	Phe	Pro														
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cag	gag	gag	tac	ccg	aga	aag	aac	tcc	atc	cag	ctg	tct	gcc	aaa	acc														
Gln	Glu	Glu	Tyr	Pro	Arg	Lys	Asn	Ser	Ile	Gln	Leu	Ser	Ala	Lys	Thr														
			695				700					705																	
atc	aag	cag	aac	agc	cgc	aat	ggg	gtg	gtc	aaa	gtt	gtc	ttc	atc	ctc														
Ile	Lys	Gln	Asn	Ser	Arg	Asn	Gly	Val	Val	Lys	Val	Val	Phe	Ile	Leu														
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tac	aac	aac	ctg	ggc	ctc	ttc	ctg	tcc	acg	gag	aat	gcc	aca	gtg	aag														
Tyr	Asn	Asn	Leu	Gly	Leu	Phe	Leu	Ser	Thr	Glu	Asn	Ala	Thr	Val	Lys														
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ctg gcc ggc gaa gca ggc ccg ggt ggc cct ggg ggc gcc tct cta gtg	2551
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Val Asn Ser Gln Val Ile Ala Ala Ser Ile Asn Lys Glu Ser Ser Arg	
760 765 770	
gtc ttc ctc atg gac cct gtc atc ttc acc gtg gcc cac ctg gag gac	2647
Val Phe Leu Met Asp Pro Val Ile Phe Thr Val Ala His Leu Glu Asp	
775 780 785	
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Lys Asn His Phe Asn Ala Asn Cys Ser Phe Trp Asn Tyr Ser Glu Arg	
790 795 800 805	
tcc atg ctg ggc tac tgg tcg acc caa ggc tgc cgc ctg gtg gag tcc	2743
Ser Met Leu Gly Trp Ser Thr Gln Gly Cys Arg Leu Val Glu Ser	
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Asn Lys Thr His Thr Thr Cys Ala Cys Ser His Leu Thr Asn Phe Ala	
825 830 835	
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Val Leu Met Ala His Arg Glu Ile Tyr Gln Gly Arg Ile Asn Glu Leu	
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Leu Leu Ser Val Ile Thr Trp Val Gly Ile Val Ile Ser Leu Val Cys	
855 860 865	
ttg gcc atc tgc atc tcc acc ttc tgc ttc ctg cgg ggg ctg cag acc	2935
Leu Ala Ile Cys Ile Ser Thr Phe Cys Phe Leu Arg Gly Leu Gln Thr	
870 875 880 885	
gac cgc aac acc atc cac aag aac ctg tgc atc aac ctc ttc ctg gct	2983
Asp Arg Asn Thr Ile His Lys Asn Leu Cys Ile Asn Leu Phe Leu Ala	
890 895 900	
gag ctg ctc ttc ctg gtc ggg atc gac aag act cag tat gag att gcc	3031
Glu Leu Leu Phe Leu Val Gly Ile Asp Lys Thr Gln Tyr Glu Ile Ala	
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Cys Pro Ile Phe Ala Gly Leu Leu His Tyr Phe Phe Leu Ala Ala Phe	
920 925 930	
tcc tgg ctg tgc ctg gag ggc gtg cac ctc tac ctg cta cta gtg gag	3127
Ser Trp Leu Cys Leu Glu Gly Val His Leu Tyr Leu Leu Leu Val Glu	
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gtg ttt gag agc gag tat tcc cgc acc aag tac tac tac ctg ggt ggc	3175
Val Phe Glu Ser Glu Tyr Ser Arg Thr Lys Tyr Tyr Tyr Leu Gly Gly	
950 955 960 965	
tac tgc ttc ccg gcc ctg gtg gtg ggc atc gcg gct gcc att gac tac	3223
Tyr Cys Phe Pro Ala Leu Val Val Gly Ile Ala Ala Ala Ile Asp Tyr	
970 975 980	
cgc agc tac gcc acc gag aag gcc tgc tgg ctc cga gtg gac aat tac	3271
Arg Ser Tyr Gly Thr Glu Lys Ala Cys Trp Leu Arg Val Asp Asn Tyr	



985	990	995	
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ctg gtg ttc ctc atg gtg acc ctg cac aag atg atc cga agc tca tct Leu Val Phe Leu Met Val Thr Leu His Lys Met Ile Arg Ser Ser Ser 1015 1020 1025			3367
gtg ctc aag ccc gac tcc agc cgc ctg gac aac att aaa tcc tgg gcg Val Leu Lys Pro Asp Ser Ser Arg Leu Asp Asn Ile Lys Ser Trp Ala 1030 1035 1040 1045			3415
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ggc ctc ctc ttc atc aac aag gag tgc gtg gtc atg gcc tat ctc ttc Gly Leu Leu Phe Ile Asn Lys Glu Ser Val Val Met Ala Tyr Leu Phe 1065 1070 1075			3511
acc acc ttc aac gcc ttc cag ggg gtc ttc atc ttc gtc ttt cac tgc Thr Thr Phe Asn Ala Phe Gln Gly Val Phe Ile Phe Val Phe His Cys 1080 1085 1090			3559
gcc tta cag aag aag gtg cac aag gag tac agc aag tgc ctg cgt cac Ala Leu Gln Lys Lys Val His Lys Glu Tyr Ser Lys Cys Leu Arg His 1095 1100 1105			3607
tcc tac tgc tgc atc cgc tcc cca ccc ggg ggc act cac gga tcc ctc Ser Tyr Cys Cys Ile Arg Ser Pro Pro Gly Gly Thr His Gly Ser Leu 1110 1115 1120 1125			3655
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 Phe Pro Pro Gly Asp Gly Gly Pro Glu Pro Pro Arg Gly Arg Asn Leu  
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gcc gat gcg gcg gcc ttt gag aag atg atc atc tca gag ctg gtg cac 4135  
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tac ctg gca gcc cca ggc ctt gag ggg cca ggg ccc gat ggg gac ggg 4663  
 Tyr Leu Ala Ala Pro Gly Leu Glu Gly Pro Gly Pro Asp Gly Asp Gly  
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 Gln Met Gln Leu Val Thr Ser Leu  
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<211> 1469

<212> PRT

<213> Homo sapiens

<400> 58

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			20					25					30		
Gly	Leu	Met	Arg	Arg	Glu	Leu	Ala	Cys	Glu	Gly	Tyr	Pro	Ile	Glu	Leu
		35					40					45			
Arg	Cys	Pro	Gly	Ser	Asp	Val	Ile	Met	Val	Glu	Asn	Ala	Asn	Tyr	Gly
	50					55					60				
Arg	Thr	Asp	Asp	Lys	Ile	Cys	Asp	Ala	Asp	Pro	Phe	Gln	Met	Glu	Asn
	65				70					75				80	
Val	Gln	Cys	Tyr	Leu	Pro	Asp	Ala	Phe	Lys	Ile	Met	Ser	Gln	Arg	Cys
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Asn	Asn	Arg	Thr	Gln	Cys	Val	Val	Val	Ala	Gly	Ser	Asp	Ala	Phe	Pro
			100					105					110		
Asp	Pro	Cys	Pro	Gly	Thr	Tyr	Lys	Tyr	Leu	Glu	Val	Gln	Tyr	Asp	Cys
		115					120					125			
Val	Pro	Tyr	Ile	Phe	Val	Cys	Pro	Gly	Thr	Leu	Gln	Lys	Val	Leu	Glu
	130					135					140				

Pro Thr Ser Thr His Glu Ser Glu His Gln Ser Gly Ala Trp Cys Lys  
 145 150 155 160  
 Asp Pro Leu Gln Ala Gly Asp Arg Ile Tyr Val Met Pro Trp Ile Pro  
 165 170 175  
 Tyr Arg Thr Asp Thr Leu Thr Glu Tyr Ala Ser Trp Glu Asp Tyr Val  
 180 185 190  
 Ala Ala Arg His Thr Thr Thr Tyr Arg Leu Pro Asn Arg Val Asp Gly  
 195 200 205  
 Thr Gly Phe Val Val Tyr Asp Gly Ala Val Leu Tyr Asn Lys Glu Arg  
 210 215 220  
 Thr Arg Asn Ile Val Lys Tyr Asp Leu Arg Thr Arg Ile Lys Ser Gly  
 225 230 235 240  
 Glu Thr Val Ile Asn Thr Ala Asn Tyr His Asp Thr Ser Pro Tyr Arg  
 245 250 255  
 Trp Gly Gly Lys Thr Asp Ile Asp Leu Ala Val Asp Glu Asn Gly Leu  
 260 265 270  
 Trp Val Ile Tyr Ala Thr Glu Gly Asn Asn Gly Arg Leu Val Val Ser  
 275 280 285  
 Gln Leu Asn Pro Tyr Thr Leu Arg Phe Glu Gly Thr Trp Glu Thr Gly  
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 Tyr Asp Lys Arg Ser Ala Ser Asn Ala Phe Met Val Cys Gly Val Leu  
 305 310 315 320  
 Tyr Val Leu Arg Ser Val Tyr Val Asp Asp Asp Ser Glu Ala Ala Gly  
 325 330 335  
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 Val Ser Leu Thr Phe Pro Asn Pro Tyr Gln Phe Ile Ser Ser Val Asp  
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 Tyr Asn Pro Arg Asp Asn Gln Leu Tyr Val Trp Asn Asn Tyr Phe Val  
 370 375 380  
 Val Arg Tyr Ser Leu Glu Phe Gly Pro Pro Asp Pro Ser Ala Gly Pro  
 385 390 395 400  
 Ala Thr Ser Pro Pro Leu Ser Thr Thr Thr Thr Ala Arg Pro Thr Pro  
 405 410 415  
 Leu Thr Ser Thr Ala Ser Pro Ala Ala Thr Thr Pro Leu Arg Arg Ala  
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 Pro Leu Thr Thr His Pro Val Gly Ala Ile Asn Gln Leu Gly Pro Asp  
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 450 455 460  
 Pro Asn Leu His Val Ser Pro Glu Leu Phe Cys Glu Pro Arg Glu Val  
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 Pro Cys Pro Lys Gly Thr Arg Gly Ile Ala Ser Phe Gln Cys Leu Pro  
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 Ser Pro Trp Val Asn Gln Val Ala Gln Lys Ile Lys Ser Gly Glu Asn  
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 545 550 555 560  
 Tyr Ala Gly Asp Val Ser Ser Ser Val Lys Leu Met Glu Gln Leu Leu  
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 Asp Ile Leu Asp Ala Gln Leu Gln Ala Leu Arg Pro Ile Glu Arg Glu  
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 Ser Ala Gly Lys Asn Tyr Asn Lys Met His Lys Arg Glu Arg Thr Cys  
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 Pro Glu Ala Leu Glu Ser Trp Lys Asp Met Asn Ala Thr Glu Gln Val  
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 His Thr Ala Thr Met Leu Leu Asp Val Leu Glu Glu Gly Ala Phe Leu  
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 Leu Ser Ala Lys Thr Ile Lys Gln Asn Ser Arg Asn Gly Val Val Lys  
 705 710 715 720  
 Val Val Phe Ile Leu Tyr Asn Asn Leu Gly Leu Phe Leu Ser Thr Glu  
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 Gly Ala Ser Leu Val Val Asn Ser Gln Val Ile Ala Ala Ser Ile Asn  
 755 760 765  
 Lys Glu Ser Ser Arg Val Phe Leu Met Asp Pro Val Ile Phe Thr Val  
 770 775 780  
 Ala His Leu Glu Asp Lys Asn His Phe Asn Ala Asn Cys Ser Phe Trp  
 785 790 795 800  
 Asn Tyr Ser Glu Arg Ser Met Leu Gly Tyr Trp Ser Thr Gln Gly Cys  
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Arg Leu Val Glu Ser Asn Lys Thr His Thr Thr Cys Ala Cys Ser His  
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 Arg Ile Asn Glu Leu Leu Leu Ser Val Ile Thr Trp Val Gly Ile Val  
 850 855 860  
 Ile Ser Leu Val Cys Leu Ala Ile Cys Ile Ser Thr Phe Cys Phe Leu  
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 Arg Gly Leu Gln Thr Asp Arg Asn Thr Ile His Lys Asn Leu Cys Ile  
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 Gln Tyr Glu Ile Ala Cys Pro Ile Phe Ala Gly Leu Leu His Tyr Phe  
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 Phe Leu Ala Ala Phe Ser Trp Leu Cys Leu Glu Gly Val His Leu Tyr  
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 Tyr Tyr Leu Gly Gly Tyr Cys Phe Pro Ala Leu Val Val Gly Ile Ala  
 965 970 975  
 Ala Ala Ile Asp Tyr Arg Ser Tyr Gly Thr Glu Lys Ala Cys Trp Leu  
 980 985 990  
 Arg Val Asp Asn Tyr Phe Ile Trp Ser Phe Ile Gly Pro Val Ser Phe  
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 Phe Val Phe His Cys Ala Leu Gln Lys Lys Val His Lys Glu Tyr Ser  
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 Lys Cys Leu Arg His Ser Tyr Cys Cys Ile Arg Ser Pro Pro Gly Gly  
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 Tyr Thr Gly Thr Gln Ser Arg Ile Arg Arg Met Trp Asn Asp Thr Val  
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Arg Lys Gln Thr Glu Ser Ser Phe Met Ala Gly Asp Ile Asn Ser Thr  
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 Pro Thr Leu Asn Arg Gly Thr Met Gly Asn His Leu Leu Thr Asn Pro  
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 Val Leu Gln Pro Arg Gly Gly Thr Ser Pro Tyr Asn Thr Leu Ile Ala  
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 Glu Ser Val Gly Phe Asn Pro Ser Ser Pro Pro Val Phe Asn Ser Pro  
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 1285 1290 1295  
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 Gly Glu Glu Glu Ala Gly Gly Pro Gly Gly Ala Asp Arg Ala Glu Ile  
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 Glu Leu Leu Tyr Lys Ala Leu Glu Glu Pro Leu Leu Leu Pro Arg Ala  
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 Pro Asp Ser Ser Pro Glu Gly Pro Ser Glu Ala Leu Pro Pro Pro Pro  
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 Pro Leu Asn Gly Asn His Gly Asn Ser Tyr Ser Ile Ala Ser Gly Glu  
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 Glu Thr Ala Leu Glu Lys Lys Ile Leu Lys Glu Leu Thr Ser Asn Tyr  
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 115 120 125  
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 Pro Arg Val Tyr Ser Thr Glu Asn His Gln Pro His His Tyr Thr Arg  
 130 135 140  
 agg cgg atc ccc caa gac cac agt gag agc ttt ttc cct ttg cta acc 480  
 Arg Arg Ile Pro Gln Asp His Ser Glu Ser Phe Phe Pro Leu Leu Thr  
 145 150 155 160  
 aac gag cag aca gaa gat ctc cag tca ccc cat aga gac tct ctc tat 528  
 Asn Glu Gln Thr Glu Asp Leu Gln Ser Pro His Arg Asp Ser Leu Tyr  
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 acc agc atg ccg aca ctg gct ggt gtg gcc gcc aca gag agt gtt acc 576  
 Thr Ser Met Pro Thr Leu Ala Gly Val Ala Ala Thr Glu Ser Val Thr  
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 acc agc acc cag acc gaa ccc cca ccg gcc aaa tgt ggt gat gcc gaa 624  
 Thr Ser Thr Gln Thr Glu Pro Pro Pro Ala Lys Cys Gly Asp Ala Glu  
 195 200 205  
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Asp Val Tyr Tyr Lys Ser Met Pro Asn Leu Gly Ser Arg Asn His Val  
 210 215 220  
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 His Gln Leu His Thr Tyr Tyr Gln Leu Gly Arg Gly Ser Ser Asp Gly  
 225 230 235 240  
 ttt ata gtt cct cca aac aaa gat ggg acc cct ccc gag gga agt tca 768  
 Phe Ile Val Pro Pro Asn Lys Asp Gly Thr Pro Pro Glu Gly Ser Ser  
 245 250 255  
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 Lys Gly Pro Ala His Leu Val Thr Ser Leu  
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 Tyr Leu Ser Asn Cys Val Gln Ile Ile Asp Arg Gly Tyr Asn His Asn  
 35 40 45  
 Glu Thr Ala Leu Glu Lys Lys Ile Leu Lys Glu Leu Thr Ser Asn Tyr  
 50 55 60  
 Ile Pro Ser Tyr Leu Asn Asn His Glu Arg Ser Ser Glu Gln Asn Arg  
 65 70 75 80

Asn Leu Met Asn Lys Leu Val Asn Asn Leu Gly Ser Gly Arg Glu Asp  
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 Asp Ala Ile Val Leu Asp Asp Ala Thr Ser Phe Asn His Glu Glu Ser  
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 His Gln Leu His Thr Tyr Tyr Gln Leu Gly Arg Gly Ser Ser Asp Gly  
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&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 64

Cys Pro Glu Gly Ser Ser Lys Gly Pro Ala His Leu Val Thr Ser Leu  
1 5 10 15

# INTERNATIONAL SEARCH REPORT

National Application No.  
PCT/US 99/04676

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/715 C12N5/10 C07K16/18 C12N5/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAVLETOV, B.A. ET AL.: "Isolation and biochemical characterization of a Ca <sup>2+</sup> -independent alpha-latrotoxin-binding protein" JOURNAL OF BIOLOGICAL CHEMISTRY (MICROFILMS), vol. 271, no. 38, 20 September 1996, pages 23239-23245, XP002066458 MD US	1,3-57
A	see the whole document --- -/--	2,12

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 June 1999

Date of mailing of the international search report

07/07/1999

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

National Application No.

PCT/US 99/04676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRASNOPIEROV, V.G. ET AL.: "alpha-latrotoxin stimulates exocytosis by the interaction with a neuronal G-protein-coupled receptor" NEURON, vol. 18, no. 6, June 1997, pages 925-937, XP002107074	11
A	see the whole document ---	2
P,X	WHITE, G.R.M. ET AL.: "Isolation and characterisation of a human homologue of the latrophilin gene from a region of 1p31.1 implicated in breast cancer" ONCOGENE, vol. 17, no. 26, 31 December 1998, pages 3513-3519, XP002107075 see the whole document	1,2,7,8
T	& WHITE, G. R. M. ET AL.: "Erratum : Isolation and characterization of a human homologue of the latrophilin gene from a region of 1p31.1 implicated in breast cancer" ONCOGENE, vol. 18, no. 12, 25 March 1999, page 2167 see the whole document ---	1
P,A	WO 98 39440 A (UNIV NEW YORK) 11 September 1998 see the whole document ---	1
P,A	US 5 759 804 A (GODISKA RONALD ET AL) 2 June 1998 see the whole document ---	1
T	MATSUSHITA, H. ET AL.: "The latrophilin family: multiply spliced G protein-couples receptors with differential tissue distribution" FEBS LETTERS., vol. 443, no. 3, 29 January 1999, pages 348-352, XP002107076 AMSTERDAM NL see the whole document -----	1,2

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 04676

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
Claims 34 and 35 were not completely searched because the subject matter was not completely disclosed
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/04676

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9839440	A	11-09-1998	AU 6685398 A	22-09-1998
US 5759804	A	02-06-1998	AT 164884 T	15-04-1998
			CA 2128208 A	09-06-1994
			DE 69317883 D	14-05-1998
			DE 69317883 T	12-11-1998
			EP 0630405 A	28-12-1994
			EP 0846762 A	10-06-1998
			ES 2118372 T	16-09-1998
			JP 7503145 T	06-04-1995
			WO 9412635 A	09-06-1994